PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/40, 31/425, 31/445, 31/495, C07D 405/06, 487/16

A1

(11) International Publication Number: WO 96/29073

(43) International Publication Date: 26 September 1996 (26.09.96)

(21) International Application Number: PCT/US96/03611

(22) International Filing Date: 15 March 1996 (15.03.96)

(30) Priority Data:

08/406,619	20 March 1995 (20.03.95)	US
08/606,312	11 March 1996 (11.03.96)	US

(60) Parent Applications or Grants
(63) Related by Continuation
US 08/406,619 (CIP)
Filed on 20 March 1995 (20.03.95)
US 08/606,312 (CIP)
Filed on 11 March 1996 (11.03.96)

(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MEINKE, Peter, T. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHIH, Thomas [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FISHER, Michael, H. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: NODULISPORIC ACID DERIVATIVES

(57) Abstract

The present invention relates to novel nodulisporic acid derivatives, which are acaricidal, antiparasitic, insecticidal and anthelmintic agents.

TITLE OF THE INVENTION

NODULISPORIC ACID DERIVATIVES

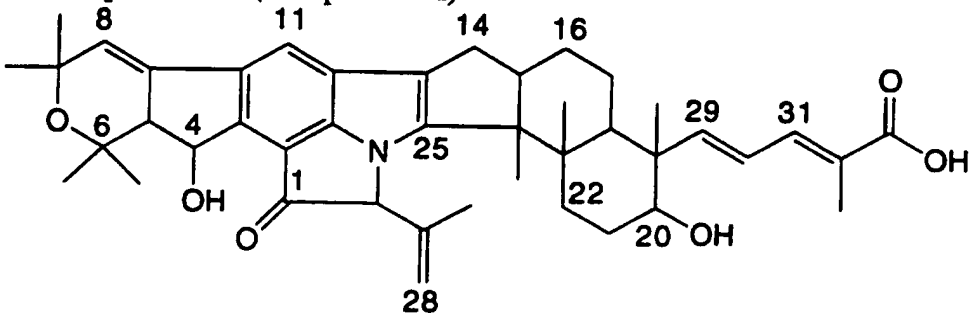
CROSS REFERENCE

This is a continuation-in part of co-pending application U.S.S.N. 08/406,619, filed March 20, 1995, which is hereby incorporated by reference.

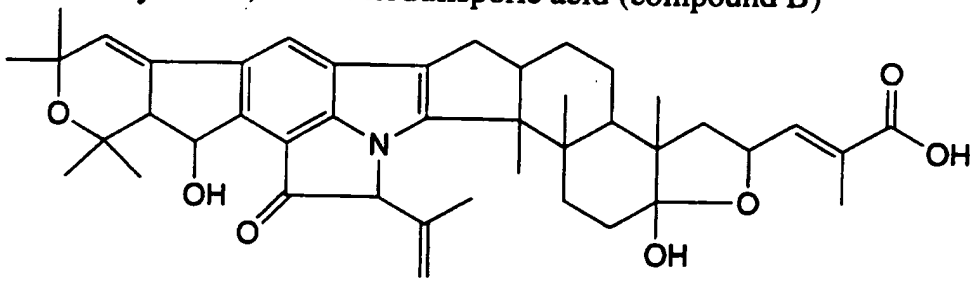
BACKGROUND OF THE INVENTION

Nodulosporic acid and two related components are antiparasitic agents and ectoparasiticidal agents isolated from the fermentation culture of *Nodulisporium* sp. MF-5954 (ATCC 74245). These three compounds have the following structures:

nodulisporic acid (compound A)



29,30-dihydro-20,30-oxa-nodulisporic acid (compound B)



(4) optionally substituted C_2-C_{10} alkynyl,
(5) optionally substituted C_3-C_8 cycloalkyl,
(6) optionally substituted C_5-C_8 cycloalkenyl
where the substitutents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from
(i) C_1-C_5 alkyl,
(ii) X-C_1-C_{10} alkyl, where X is O or $S(O)_m$.
(iii) C_3-C_8 cycloalkyl,
(iv) hydroxy,
(v) halogen,
(vi) cyano,
(vii) carboxy,
(viii) NY^1Y^2, where Y^1 and Y^2 are independently H or C_1-C_{10} alkyl,
(ix) C_1-C_{10} alkanoylamino, and
(x) aroyl amino wherein said aroyl is optionally substituted with 1 to 3 groups independently selected from R^f
(7) aryl C_0-C_5 alkyl wherein said aryl is optionally substituted with 1 to 3 groups independently selected from R^f,
(8) C_1-C_5 perfluoroalkyl
(9) a 5- or 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen atoms optionally substituted by 1 to 3 groups independently selected from hydroxy, oxo, C_1-C_{10} alkyl and halogen, and which may be saturated or partly unsaturated,

R_2, R_3, and R_4 are independently OR^a, OCO_2R^b, $OC(O)NR^cR^d$; or
R_1+R_2 represent =O, $=NOR^a$ or $=N\text{-}NR^cR^d$;
R_5 and R_6 are H; or
R_5 and R_6 together represent -O-;
R_7 is (1) CHO, or

(13) optionally substituted C_3-C_8 cycloalkyl
(14) optionally substituted C_5-C_8 cycloalkenyl
where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl, cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl are from 1 to 10 groups independently selected from hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, aryl C_1-C_3 alkoxy, NR^gR^h, CO_2R^b, $CONR^cR^d$ and halogen,
(15) C_1-C_5 perfluoroalkyl,
(16) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from C_1-C_5 alkyl, C_1-C_5 perfluoroalkyl, nitro, halogen and cyano,
(17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from C_1-C_5 alkyl, C_1-C_5 alkenyl, C_1-C_5 perfluoroalkyl, amino, $C(O)NR^cR^d$, cyano, CO_2R^b and halogen, and which may be saturated or partly unsaturated;

R^b is
(1) H,
(2) optionally substituted aryl,
(3) optionally substituted C_1-C_{10} alkyl,
(4) optionally substituted C_3-C_{10} alkenyl,
(5) optionally substituted C_3-C_{10} alkynyl,
(6) optionally substituted C_3-C_{15} cycloalkyl,
(7) optionally substituted C_5-C_{10} cycloalkenyl, or
(8) optionally substituted 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;
where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from
(i) hydroxy,
(ii) C_1-C_6 alkyl,
(iii) oxo,

to 3 groups independently selected from R^g, hydroxy, thioxo and oxo;

R^e is
(1) halogen,
(2) C_1-C_7 alkyl,
(3) C_1-C_3 perfluoroalkyl,
(4) $-S(O)_mR^i$,
(5) cyano,
(6) nitro,
(7) $R^iO(CH_2)_v$-,
(8) $R^iCO_2(CH_2)_v$-,
(9) $R^iOCO(CH_2)_v$,
(10) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or hydroxy,
(11) $SO_2NR^gR^h$, or
(12) amino;

R^f is
(1) C_1-C_4 alkyl,
(2) X-C_1-C_4 alkyl, where X is O or $S(O)_m$,
(3) C_2-C_4 alkenyl,
(4) C_2-C_4 alkynyl,
(5) C_1-C_3-perfluoroalkyl,
(6) NY^1Y^2, where Y^1 and Y^2 are independently H or C_1-C_5 alkyl,
(7) hydroxy,
(8) halogen, and
(9) C_1-C_5 alkanoyl amino,

R^g and R^h are independently
(1) hydrogen,
(2) C_1-C_6 alkyl optionally substituted with hydroxy , amino, or CO_2R^i
(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7 alkoxy, C_1-C_7 alkyl or C_1-C_3 perfluoroalkyl,

(6) optionally substituted C_5-C_6 cycloalkenyl

where the substitutents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from

(i) C_1-C_3 alkyl,
(ii) X-C_1-C_6 alkyl, where X is O or $S(O)_m$,
(iii) C_5-C_6 cycloalkyl,
(iv) hydroxy,
(v) halogen,
(vi) cyano,
(vii) carboxy, and
(viii) NY^1Y^2, where Y^1 and Y^2 are independently H or C_1-C_6 alkyl,

(7) aryl C_0-C_3 alkyl wherein said aryl is optionally substituted with 1 to 3 groups independently selected from R^f,

(8) C_1-C_3 perfluoroalkyl,

(9) a 5- or 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen atoms optionally substituted by 1 to 3 groups independently selected from hydroxy, oxo, C_1-C_6 alkyl and halogen, and which may be saturated or partly unsaturated,

R_8 is (1) H,
(2) OH, or
(3) NH_2;

R_9 is (1) H or
(2) OH;

R_{10} is (1) $C(O)OR^b$,
(2) $C(O)N(OR^b)R^c$,
(3) $C(O)NR^cR^d$,
(4) $NHC(O)OR^b$,
(5) $NHC(O)NR^cR^d$,
(6) CH_2OR^a,
(7) $CH_2OCO_2R^b$,

(2) optionally substituted aryl,
(3) optionally substituted C_1-C_7 alkyl,
(4) optionally substituted C_3-C_7 alkenyl,
(5) optionally substituted C_3-C_7 alkynyl,
(6) optionally substituted C_5-C_7 cycloalkyl,
(7) optionally substituted C_5-C_7 cycloalkenyl, or
(8) optionally substituted 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;

where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from

(i) hydroxy,
(ii) C_1-C_3 alkyl,
(iii) oxo,
(iv) $SO_2NR^gR^h$,
(v) aryl C_1-C_3 alkoxy,
(vi) hydroxy C_1-C_3 alkyl,
(vii) C_1-C_7 alkoxy,
(viii) hydroxy C_1-C_3 alkoxy,
(ix) amino C_1-C_3 alkoxy,
(x) cyano,
(xi) C_1-C_3 perfluoroalkyl,
(xii) C_1-C_3 alkyl-S(O)m,
(xiii) C_5-C_6 cycloalkyl optionally substituted with 1 to 4 groups independently selected from R^e,
(xiv) C_5-C_6 cycloalkenyl,
(xv) halogen,
(xvi) C_1-C_3 alkanoyloxy,
(xvii) $C(O)NR^gR^h$,
(xviii) CO_2R^i,
(xix) optionally substituted aryl C_1-C_3 alkoxy,

wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R^e,

(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7 alkoxy, C_1-C_7 alkyl or C_1-C_3 perfluoroalkyl,

(4) aryl C_1-C_6 alkyl, wherein the aryl is optionally substituted with C1-C3 perfluorolkyl or 1,2-methylenedioxy;

(5) C_1-C_5 alkoxycarbonyl,

(6) C_1-C_5 alkanoyl,

(7) C_1-C_5 alkanoyl C_1-C_6 alkyl,

(9) aryl C_1-C_5 alkoxycarbonyl,

(10) aminocarbonyl,

(11) C_1-C_5 monoalkylaminocarbonyl

(12) C_1-C_5 dialkylaminocarbonyl; or

R^g and R^h together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, $S(O)_m$, and N, optionally substituted with 1 to 3 groups independently selected from R^e and oxo;

R^i is (1) hydrogen,

(2) C_1-C_3 perfluoroalkyl,

(3) C_1-C_4 alkyl,

(4) optionally substituted aryl C_0-C_4 alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, and hydroxy;

all other variables are as defined under Formula I.

In another preferred embodiment, the present invention provides compounds of Formula I wherein

R_1 is (1) hydrogen,

(2) optionally substituted C_1-C_3 alkyl,

(3) optionally substituted C_2-C_3 alkenyl,

(4) optionally substituted C_2-C_3 alkynyl,

where the substitutents on the alkyl, alkenyl, and alkynyl are 1 to 3 groups independently selected from

(i) methyl,

from hydroxy, C_1-C_2 alkoxy, aryl C_1-C_3 alkoxy, NR^gR^h, CO_2R^b, $CONR^cR^d$ and halogen,

(10) trifluoromethyl,

(11) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from methyl, trifluoromethyl and halogen,

(12) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from methyl, trifluoromethyl, $C(O)NR^cR^d$, CO_2R^b and halogen, and which may be saturated or partly unsaturated;

R^b is (1) H,

(2) optionally substituted aryl,

(3) optionally substituted C_1-C_6 alkyl,

(4) optionally substituted C_3-C_6 alkenyl,

(5) optionally substituted C_3-C_6 alkynyl,

(6) optionally substituted C_5-C_6 cycloalkyl,

(7) optionally substituted C_5-C_6 cycloalkenyl, or

(8) optionally substituted 5- to 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;

where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from

(i) hydroxy,

(ii) C_1-C_3 alkyl,

(iii) oxo,

(iv) $SO_2NR^gR^h$,

(v) aryl C_1-C_3 alkoxy,

(vi) hydroxy C_1-C_4 alkyl,

(vii) C_1-C_4 alkoxy,

(viii) hydroxy C_1-C_4 alkoxy,

(ix) amino C_1-C_4 alkoxy,

(11) amino;

R^f is (1) methyl,

(2) X-C_1-C_2 alkyl, where X is O or $S(O)_m$,

(3) trifluoromethyl,

(4) NY^1Y^2, where Y^1 and Y^2 are independently H or methyl,

(5) hydroxy,

(6) halogen, and

(7) acetylamino,

R^g and R^h are independently

(1) hydrogen,

(2) C_1-C_6 alkyl optionally substituted with hydroxy , amino, or CO_2R^i

(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7 alkoxy, C_1-C_7 alkyl or C_1-C_3 perfluoroalkyl,

(4) aryl C_1-C_6 alkyl, wherein the aryl is optionally substituted with C1-C3 perfluorolkyl or 1,2-methylenedioxy;

(5) C_1-C_5 alkoxycarbonyl,

(6) C_1-C_5 alkanoyl,

(7) C_1-C_5 alkanoyl C_1-C_6 alkyl,

(9) aryl C_1-C_5 alkoxycarbonyl,

(10) aminocarbonyl,

(11) C_1-C_5 monoalkylaminocarbonyl

(12) C_1-C_5 dialkylaminocarbonyl; or

R^g and R^h together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, $S(O)_m$, and N, optionally substituted with 1 to 3 groups independently selected from R^e and oxo;

R^i is (1) hydrogen,

(2) C_1-C_3 perfluoroalkyl,

(3) C_1-C_4 alkyl,

(4) optionally substituted aryl C_0-C_6 alkyl, where the aryl substituents are from 1 to 3 groups independently

"Alkyl" as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as benzofused carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "halogen" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

The term "heterocycle", unless otherwise specfied, means mono- or bicyclic compounds that are saturated or partly unsaturated, as well as benzo- or heteroaromatic ring fused saturated heterocycles or partly unsaturated heterocycles, and containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen. Examples of saturated heterocycles include morpholine, thiomorpholine, piperidine, piperazine, tetrahydropyran, tetrahydrofuran, dioxane, tetrahydrothiophene, oxazolidine, pyrrolidine; examples of partly unsaturated heterocycles include dihydropyran, dihydropyridazine, dihydrofuran, dihydrooxazole, dihydropyrazole, dihydropyridine, dihydropyridazine and the like. Examples of benzo- or heteroaromatic ring fused heterocycle include 2,3-dihydrobenzofuranyl, benzopyranyl, tetrahydroquinoline, tetrahydroisoquinoline, benzomorpholinyl, 1,4-benzodioxanyl, 2,3-dihydrofuro(2,3-b)pyridyl and the like.

ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

Compounds of the present invention are named based on the trivial name of the parent compound, nodulisporic acid (compound A), and their position numbers are those as indicated in formula I.

Compounds of the present invention are prepared from the three nodulisporic acids (Compounds A, B and C), which in turn are obtained from the fermentation culture of *Nodulisporium* sp. MF-5954 (ATCC 74245). The description of the producing microorganism, the fermentation process, and the isolation and purification of the three nodulisporic acids are disclosed in US Patent 5,399,582, issued March 21, 1995, which is hereby incorporated by reference in its entirety.

in a protic solvent such as methanol, ethanol, water, tetrahydrofuran/water or dimethylformamide/water and the like at from 0°C to the reflux temperature of the solution. Alternatively, the resultant esters may be hydrolyzed by treatment with a Lewis acid, such as magnesium chloride, aluminum chloride, titanium tetra-isopropoxide and the like in a protic solvent such as methanol, ethanol, isopropanol and the like and the reactions are complete in from 1 to 24 hours at 0°C to the reflux temperature of the solution.

During certain reactions described below, it may be necessary to protect the groups at R_2, R_3, R_4, R_8, R_9 and R_{10}. With these positions protected, the reactions may be carried out at other positions without affecting the remainder of the molecule. Subsequent to any of the described reactions (vida infra), the protecting group(s) may be removed and the unprotected product isolated. The protecting groups employed at R_2, R_3, R_4, R_8, R_9 and R_{10} are those which may be readily synthesized, not significantly affected by the reactions at the other positions, and may be removed without significantly affecting any other functionality of the molecule. One preferred type of protecting group is the tri-substituted silyl group, preferably the tri-loweralkyl silyl group or di-loweralkyl-aryl silyl group. Especially preferred examples are the trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldimethylsilyl and dimethylphenylsilyl groups.

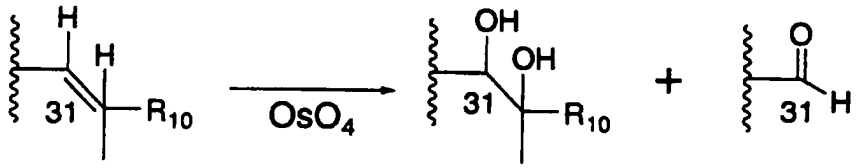
The protected compound may be prepared with the appropriately substituted silyl trifluoromethanesulfonate or silyl halide, preferably the silyl chloride. The reaction is carried out in an aprotic solvent such as methylene chloride, benzene, toluene, ethyl acetate, isopropyl acetate, tetrahydrofuran, dimethylformamide and the like. In order to minimize side reactions, there is included in the reaction mixture a base to react with the acid released during the course of the reaction. Preferred bases are amines such as imidazole, pyridine, triethylamine or diisopropylethylamine and the like. The base is required in amounts equimolar to the amount of hydrogen halide liberated, however, generally several equivalents of the amine are employed. The reaction is stirred at

oxo analog with $H_2NNR^cR^d$ to give the corresponding hydrazones using conditions directly analogous to those described for oxime formation.

Compounds of formula I wherein one or both of the ---- bonds represent a single bond may be prepared from the corresponding compound wherein ---- is a double bond by conventional hydrogenation procedures. The double bonds may be hydrogenated with any of a variety of standard precious metal hydrogenation catalysts such as Wilkinson's catalyst, Pearlman's catalyst, 1-25% palladium on carbon, 1-25% platinum on carbon and the like. The reaction is generally carried out in a non-reducible solvents (either protic or aprotic) such as methanol, ethanol, isopropanol, tetrahydrofuran, ethyl acetate, isopropyl acetate, benzene, toluene, dimethylformamide and the like. The hydrogen source may be hydrogen gas from 1 to 50 atmospheres of pressure or other hydrogen sources such as ammonium formate, cyclohexene, cyclohexadiene and the like. The reduction also may be carried out using sodium dithionite and sodium bicarbonate in the presence of a phase transfer catalyst, in particular a tetraalkylammonium phase transfer catalyst, and the like. The reactions may be run from 0°C to 100°C and are complete in from 5 min to 24 hours.

Compounds of formula I wherein R_8 and R_9 are both hydroxyl groups may be prepared according to the procedure shown in Scheme I.

SCHEME I



II III IV

Thus, Compound II is treated with osmium tetroxide under conditions known to those skilled in the art to yield the diol product III. Also produced during this reaction is the aldehyde IV. Osmium tetroxide may

borohydride and the like. Compounds of formula I wherein R_2 and R_1 together are oxo and R_{10} is CH_2OH may be obtained by reacting the appropriate carboxylic acid (e.g., where R10 is CO_2H) with less reactive reducing agents such as diborane and the like.

Compounds of formula I wherein R_2 is OH and R_1 is other than H, may be prepared from the corresponding ketone by treating the appropriate oxo analog with a Grignard reagent R_1MgBr, or with a lithium reagent R_1Li. These reactions are performed in a manner known to those skilled in the art and preferably are performed in aprotic solvents such as diethyl ether, tetrahydrofuran, hexanes or pentanes. The reactions are complete in from 5 minutes to 24 hours at temperatures ranging from -78°C to 60°C.

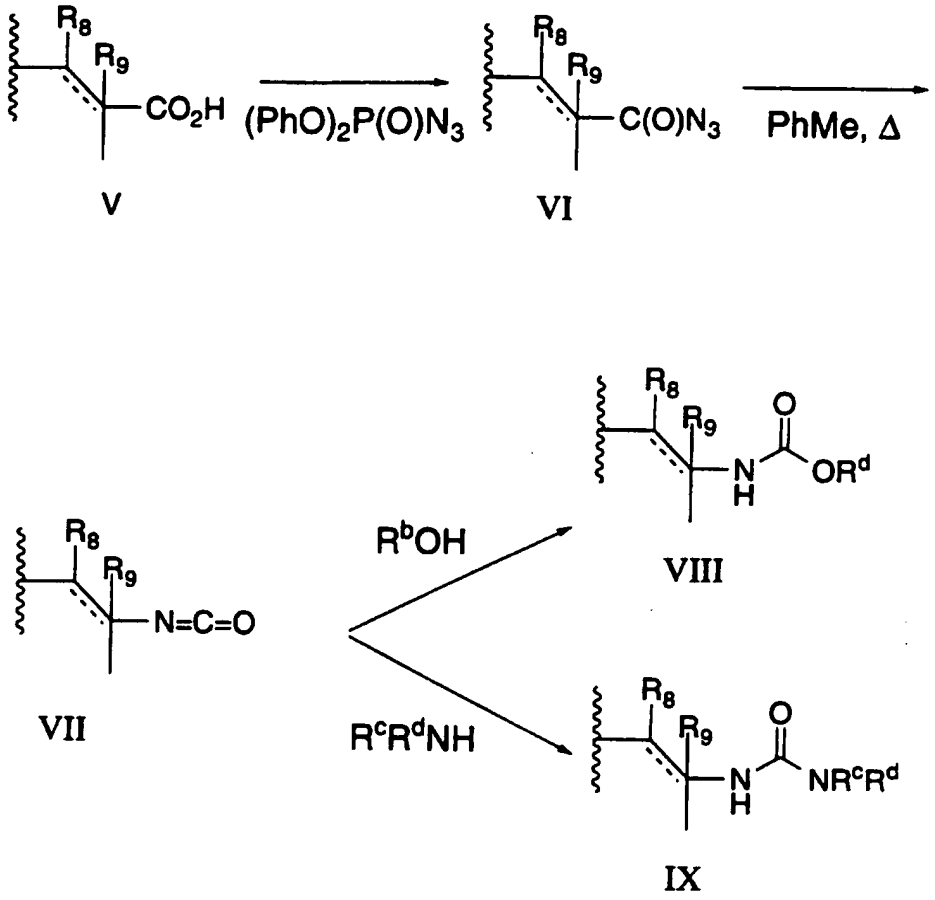
Compounds of formula I where R_{10} is $C(O)N(OR^b)R^c$ or $C(O)NR^cR^d$ are prepared from the corresponding carboxylic acid using standard amide-forming reagents known to those skilled in the art. The reaction is carried out using at least one equivalent of an amine nucleophile, $HN(OR^b)R^c$ or HNR^cR^d, although preferably ten to one hundred equivalents of amine nucleophiles are employed. Amide-forming reagents include, but are not restricted to, dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl), diisopropylcarbodiimide, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorphosphate (BOP), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), chloro-tris-pyrrolidino-phosphonium hexafluorophosphate (PyCloP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), diphenylphosphoryl azide (DPPA), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-benzotriazol-1-yl-N,N,N',N'-bis(pentamethylene)uronium hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The amide-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole or N-hydroxy-7-aza-benzotriazole. The amidation reaction is generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as

hexafluorophosphate and 2-chloro-1-methylpyridinium iodide. The ester-forming reactions may be facilitated by the optional addition of N-hydroxybenzotriazole, N-hydroxy-7-aza-benzotriazole, 4-(N,N-dimethylamino)pyridine or 4-pyrrolidinopyridine. The reaction is generally performed using at least one equivalent (although several equivalents may be employed) of amine bases such as triethylamine, diisopropylethylamine, pyridine and the like. The carboxyl group may be activated for ester bond formation via its corresponding acid chloride or mixed anhydride, using conditions known to those skilled in the art. These ester-forming reactions are carried out in aprotic solvents such as methylene chloride, tetrahydrofuran, diethyl ether, dimethylformamide, N-methylpyrrolidine and the like at temperatures ranging from -20°C to 60°C and are complete in 15 minutes to 24 hours.

Compounds of formula I wherein one or more of R_2, R_3, R_4, R_8 and R_9 is OR^a, OCO_2R^b or $OC(O)NR^cR^d$, and/or where R_{10} is CH_2OR^a, $CH_2OCO_2R^b$ or $CH_2OC(O)NR^cR^d$ may be prepared using known methods for acylation, sulfonylation and alkylation of alcohols. Thus, acylation may be accomplished using reagents such as acid anhydrides, acid chlorides, chloroformates, carbamoyl chlorides, isocyanates and amine bases according to general procedures known to those skilled in the art. Sulfonylations may be carried out using sulfonylchlorides or sulfonic anhydrides. The acylation and sulfonylation reactions may be carried out in aprotic solvents such as methylene chloride, chloroform, pyridine, benzene, toluene and the like. The acylation and sulfonylation reactions are complete in from 15 minutes to 24 hours at temperatures ranging from -20°C to 80°C. The degree of acylation, sulfonylation and alkylation will depend on the amount of the reagents used. Thus, for example, using one equivalent of an acylating reagent and one equivalent of nodulisporic acid results in a product mixture containg 4- and 20-acylated nodulisporic acid; such a mixture may be separated by conventional techniques such as chromatography.

Compounds of formula I wherein one or more of R_2, R_3, R_4, R_8 and R_9 is OR^a and/or where R_{10} is CH_2OR^a, may be prepared using methods known to those skilled in the art for the alkylation of

SCHEME II



In Scheme II, R_8, R_9, R^b, R^c, R^d and ---- have the same meaning as defined under formula I. Thus, the carboxylic acid (compound V) is treated with diphenylphosphoryl azide to provide the acyl azide (compound VI). Heating of compound VI in an aprotic solvent such as benzene, toluene, dimethylformamide and the like results in a rearrangement yielding compound VII, an isocyanate. Compound VII may be reacted in an aprotic solvent such as benzene, toluene, methylene chloride, 1,2-dichloroethylene, dimethylformamide and the like, with an alcohol R^bOH, such as methanol, ethanol, benzyl alcohol, 2-trimethylsilylethanol, 2,2,2-trichloroethanol, methyl glyocolate, phenol and the like to yield compound VIII, a carbamate. The addition of one or

and organs of the body such as the heart and blood vessels, subcutaneous and lymphatic tissue and the like. The parasitic infections known as helminthiases lead to anemia, malnutrition, weakness, weight loss, severe damage to the walls of the intestinal tract and other tissues and organs and, if left untreated, may result in death of the infected host. The compounds of this invention have activity against these parasites, and in addition are also active against Dirofilaria in dogs and cats, Nematospiroides, Syphacia, Aspiculuris in rodents, arthropod ectoparasites of animals and birds such as ticks, mites such as scabies lice, fleas, blowflies, and other biting insects in domesticated animals and poultry, such as Tenophalides, Ixodes, Psoroptes, and Hemotobia, in sheep Lucilia sp., biting insects and such migrating dipterous larvae as Hypoderma sp. in cattle, Gastrophilus in horses, and Cuterebra sp. in rodents and nuisance flies including blood feeding flies and filth flies.

The instant compounds are also useful against parasites which infect humans. The most common genera of parasites of the gastro-intestinal tract of man are Ancylostoma, Necator, Ascaris, Strongyloides, Trichinella, Capillaria, Trichuris, and Enterobius. Other medically important genera of parasites which are found in the blood or other tissues and organs outside the gastrointestinal tract are the filiarial worms such as Wuchereria, Brugia, Onchocerca and Loa, Dracunuculus and extra intestinal stages of the intestinal worms Strongyloides and Trichinella. The compounds are also of value against arthropods parasitizing man, biting insects and other dipterous pests causing annoyance to man.

The compounds are also active against household pests such as the cockroach, Blatella sp., clothes moth, Tineola sp., carpet beetle, Attagenus sp., the housefly Musca domestica as well as fleas, house dust mites, termites and ants.

The compounds are also useful against insect pests of stored grains such as Tribolium sp., Tenebrio sp. and of agricultural plants such as aphids, (Acyrthiosiphon sp.); against migratory orthopterans such as locusts and immature stages of insects living on plant tissue. The compounds are useful as a nematocide for the control of soil nematodes

boluses comprise the active ingredient admixed with a carrier vehicle such as starch, talc, magnesium stearate, or di-calcium phosphate.

Where it is desired to administer the instant compounds in a dry, solid unit dosage form, capsules, boluses or tablets containing the desired amount of active compound usually are employed. These dosage forms are prepared by intimately and uniformly mixing the active ingredient with suitable finely divided diluents, fillers, disintegrating agents, and/or binders such as starch, lactose, talc, magnesium stearate, vegetable gums and the like. Such unit dosage formulations may be varied widely with respect to their total weight and content of the antiparasitic agent depending upon factors such as the type of host animal to be treated, the severity and type of infection and the weight of the host.

When the active compound is to be administered via an animal feedstuff, it is intimately dispersed in the feed or used as a top dressing or in the form of pellets or liquid which may then be added to the finished feed or optionally fed separately. Alternatively, feed based individual dosage forms may be used such as a chewable treat. Alternatively, the antiparasitic compounds of this invention may be administered to animals parenterally, for example, by intraruminal, intramuscular, intravascular, intratracheal, or subcutaneous injection in which the active ingredient is dissolved or dispersed in a liquid carrier vehicle. For parenteral administration, the active material is suitably admixed with an acceptable vehicle, preferably of the vegetable oil variety such as peanut oil, cotton seed oil and the like. Other parenteral vehicles such as organic preparation using solketal, glycerol formal, propylene glycol, and aqueous parenteral formulations are also used. The active compound or compounds are dissolved or suspended in the parenteral formulation for administration; such formulations generally contain from 0.0005 to 5% by weight of the active compound.

The agents of this invention can be used in the treatment and/or prevention of diseases caused by parasites, for example, arthropod parasites such as ticks, lice, fleas, mites and other biting arthropods in domesticated animals and poultry. The agents of this invention also are useful in the prevention and treatment of diseases caused by

methods such as grinding, stirring, milling or tumbling. Compositions containing from about 0.005 to 2.0% weight of the active compound are particularly suitable as feed premixes. Feed supplements, which are fed directly to the animal, contain from about 0.0002 to 0.3% by weight of the active compounds.

Such supplements are added to the animal feed in an amount to give the finished feed the concentration of active compound desired for the treatment and control of parasitic diseases. Although the desired concentration of active compound will vary depending upon the factors previously mentioned as well as upon the particular compound employed, the compounds of this invention are usually fed at concentrations of between 0.00001 to 0.002% in the feed in order to achieve the desired anti-parasitic result.

In using the compounds of this invention, the individual compounds may be prepared and used in that form. Alternatively, mixtures of the individual compounds may be used, or they may be combined with other active compounds not related to the compounds of this invention.

The compounds of this invention are also useful in combatting agricultural pests that inflict damage upon crops while they are growing or while in storage. The compounds are applied using known techniques as sprays, dusts, emulsions and the like, to the growing or stored crops to effect protection from such agricultural pests.

Compounds of this invention may be co-administered with anthelmintic agents. These anthelmintic agents are meant to include, but not be restricted to, compounds selected from the avermectin and milbemycin class of compounds such as ivermectin, avermectin, abamectin, emamectin, eprinamectin, doramectin, fulladectin, moxidectin, Interceptor and nemadectin. Additional anthelmintic agents include the benzimidazoles such as thiabendazole, cambendazole, parbendazole, oxibendazole, mebendazole, flubendazole, fenbendazole, oxfendazole, albendazole, cyclobendazole, febantel, thiophanate and the like. Additional anthelmintic agents include imidazothiazoles and

To 0.8 mg Compound B in 1 mL methanol at room temperature was added 0.2 mL 1 M trimethylsilyldiazomethane in hexanes. After 5 minutes, 0.1 mL glacial acetic acid was added, the solution stirred for three minutes and the 2 mL saturated $NaHCO_3$ was added (foaming occurred). The solution was extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude was purifed by reversed-phase HPLC using 15:85 water/methanol as eluant and the purified product was characterized by ^1H NMR.

EXAMPLE 3

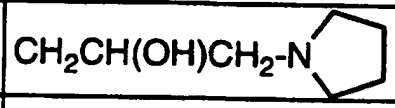
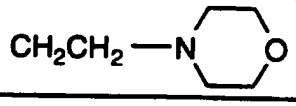
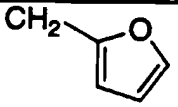
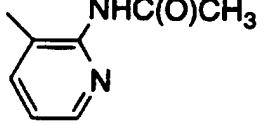
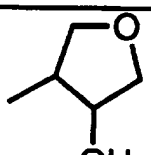
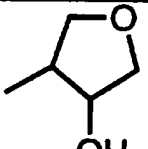
Methyl 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydronodulisporate

To 1 mg Compound C in 1 mL methanol at room temperature was added 0.2 mL 1 M trimethylsilyldiazomethane in hexanes. After 5 minutes, 0.1 mL glacial acetic acid was added, the solution stirred for three minutes and the 2 mL saturated $NaHCO_3$ was added (foaming occurred). The solution was extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude was purifed by reversed-phase HPLC using 17.5:82.5 water/methanol as eluant and the purified product was characterized by ^1H NMR.

EXAMPLE 4

Ethyl nodulisporate

To a solution containing 20 mg nodulisporic acid in 2 mL methylene chloride at room temperature was added 0.11 mL ethanol, 0.008 mL diisopropylethylamine, 1 mg N,N-dimethylaminopyridine (DMAP) followed by 13 mg BOP reagent. After 50 hours at room temperature, the solution was poured into 1/1 saturated sodium bicarbonate/brine and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, the solids were removed by filtration and the solution concentrated under reduced pressure. Pure product was obtained following preparative TLC on silica gel (one 1000 micron plate) using 1/3 acetone/hexanes as eluant. Purified product (15

14	815.4	4-Nitrobenzyl alcohol	$CH_2Ph(4\text{-}NO_2)$
15	815.4	3-Nitrobenzyl alcohol	$CH_2Ph(3\text{-}NO_2)$
16	807.7	2-Hydroxy-3-(1-pyrrolidinyl)propanol	
17	793.7	4-(2-Hydroxyethyl)-morpholine	
18	762.4	2,2,2-Trifluoroethanol	CH_2CF_3
19		2-(Hydroxymethyl)furan	
20	764.5	5-Hydroxypentan-2-one	$CH_2CH_2CH_2C(=O)CH_3$
21		3-Phenylpropanol	$CH_2CH_2CH_2Ph$
22	764.3	3,3-Dimethylbutanol	$CH_2CH_2C(CH_3)_2CH_3$
23		2-(N-Acetylamino)-3-hydroxypyridine	
24	766.7	3,4-Dihydroxytetrahydro-furan, Isomer A	 , isomer A
25	766.6	3,4-Dihydroxytetrahydro-furan, Isomer B	 , isomer B
26	831.5	1,1,1,3,3,3-hexafluoro-isopropanol	$CH(CF_3)_2$
27		2-(Trifluoromethyl)benzyl alcohol	$CH_2Ph(2\text{-}CF_3)$

EXAMPLE 28

General Procedure for the Preparation of Additional Ester Derivatives of Compounds A, B and C

(hydroxymethyl)propanol, trans-2-Hydroxycyclohexanol, 2-Hydroxy-4-methylphenol, 2-(Hydroxymethyl)pyridine, 1-Hydroxymethyl-1-cyclohexanol, 2-Hydroxyhexanol, 2-Hydroxy-1-methoxypropane, 2-(Hydroxymethyl)imidazole, 3-Hydroxymethylpyrazole, trans-4-Hydroxycyclohexanol, N-Acetyl-4-hydroxybutylamine, Hydroxycyclopentane, 2-(Methylsulfonyl)ethanol, 2-(Methylsulfinyl)ethanol, 4-(2-Hydroxyethyl)phenol, 2-(2-Hydroxyethyl)phenol, 2-Hydroxy-3-methylbutanol, 3-(N-Acetylamino)propanol, 3-(Diethylamino)propanol, 3-(Dimethylamino)propanol, Allyl alcohol, 2-(Dimethylamino)ethanol, Glycerol, 2-Methoxyethanol, 2-(N-Acetylamino)ethanol, D-(Hydroxymethyl)pyrrolidine, 3-Hydroxypyrrolidine, 2-(Hydroxyethyl)benzene, 2-Hydroxyethyl-1-methylpyrrolidine, 2-Hydroxy-2-methyl-propanol, Cyclopropanol, Cyclohexanol, 3-Hydroxypropanol, 3-Ethoxypropanol, Propargyl alcohol, Ethyl glycolate, 2-Fluoroethanol, 3-(Dodecyloxy)propanol, 4-Hydroxybutanol, 5-Hydroxypentanol, 2-(Dimethylamino)ethanol, 2-(2-Hydroxyethoxy)ethanol, 1-(2-Hydroxyethyl)imidazolone, 2-(2-Hydroxyethoxy)ethylamine, Isopropanol, 2,2,2-Trifluoroethanol, 4-Nitrobenzyl alcohol, 3-Nitrobenzyl alcohol, 2-Methoxyethanol, 4-(Hydroxyethyl)phenol, 4-(3-Hydroxypropyl)-1-sulfonamidobenzene, D,L-2-(Hydroxymethyl)tetrahydrofuran, Methyl lactate, 5-Hydroxyhexanoic acid, methyl ester, 3-Methoxypropanol, 3-Hydroxypiperidine, Pentanol, 4-Hydroxyheptane, 4-(2-Hydroxyethyl)-1,2-dimethoxybenzene, 4-Hydroxymethyl-1,2-methylenedioxybenzene, 4-(Trifluoromethyl)benzyl alcohol, 4-(Methylthio)pheno, 2-(Hydroxymethyl)furan, 5-Hydroxypentan-2-one, 2-Hydroxy-3-methyl-butanoic acid, methyl ester, 2-Hydroxy-3-phenyl-propanoic acid, ethyl ester, 1-(Hydroxymethyl)napthalene, 3-Phenylpropanol, 3,3-Dimethylbutanol, 3-(2-Hydroxyethyl)fluorobenzene, 4-Hydroxy-1-carboethoxypiperidine, (R)-2-(Hydroxymethyl)tetrahydrofuran, (S)-2-(Hydroxymethyl)tetrahydrofuran, (S)-2-Hydroxy-3-methylbutanol, (R)-2-Hydroxy-3-methylbutanol, (S)-2-Hydroxy-propanol, 3,4-Dihydroxytetrahydrofuran, 1,1,1,3,3,3-hexfluoroisopropanol, 2-

After 30 minutes at room temperature, the reaction was quenched with 2 mL saturated $NaHCO_3$, extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude was partially purified by silica gel flash chromatography using 0.5:5:95 NH_4OH/MeOH/$CHCl_3$ as eluant followed by reversed-phase HPLC purification using 20:80 water/methanol as eluant. The product was characterized by ^1H NMR.

EXAMPLE 31
4-Morpholinyl-nodulisporamide

To 1.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop morpholine and 2 mg N-hydroxybenzotriazole. 2 mg pyBOP was then added. After 1 hour at room temperature, the solution was filtered through 2 inches silica gel in a pipet without workup using ethyl acetate as eluant. The resultant solution was concentrated under reduced pressure and pure product was obtained following reversed-phase HPLC using 20:80 water/MeOH as eluant. The product was characterized by ^1H NMR.

EXAMPLE 32
N-(2-Hydroxyethyl)-nodulisporamide

To 0.5 mg nodulisporic acid in 1 mL methylene chloride at room temperature was added 2 drops diisopropylethylamine, 5 mg $H_2NCH_2CH_2OH$, 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 30 minutes, the reaction was quenched with 2 mL saturated $NaHCO_3$, extracted with ethyl acetate, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 20:80 water/methanol as eluant and the product was characterized by ^1H NMR and mass spectrometry.

EXAMPLE 33
N-(1-Methoxycarbonyl-2-hydroxyethyl)-nodulisporamide

17.5:82.5 water/methanol as eluant. The product was characterized by ^1H NMR and mass spectrometry.

EXAMPLE 36

N,N-Tetramethylene-nodulisporamide

To 125 mg nodulisporic acid in 10 mL methylene chloride at 0°C was added 0.18 mL diisopropylethylamine, 0.15 mL pyrrolidine followed by 108 mg PyBOP. After 5 minutes, the solution was warmed to room temperature. After 1.5 hours, the solution was poured in 25 mL saturated $NaHCO_3$, extracted with methylene chloride, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Pure N,N-tetramethylene-nodulisporamide was obtained following reversed-phase HPLC purification using 50:50 acetonitrile/water as eluant (isocratic for ten min), followed by a linear 30 minute gradient to 75:25 acetonitrile/water. Pure product (26 mg) was characterized by ^1H NMR and MS.

EXAMPLE 37

N-Ethyl 29,30-dihydro-20,30-oxa-nodulisporamide

To 1 mg Compound B in 1 mL methylene chloride at room temperature was added 1 drop diisopropylethylamine, 1 drop $CH_3CH_2NH_2$, 3 mg N-hydroxybenzotriazole and 3 mg PyBOP. After 15 minutes, the reaction was quenched with 2 mL saturated $NaHCO_3$, extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by reversed-phase HPLC using 15:85 water/methanol as eluant and the purified product was characterized by ^1H NMR.

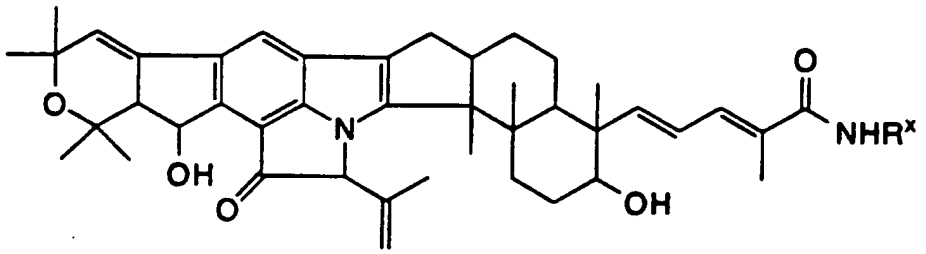
EXAMPLE 38

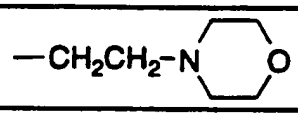
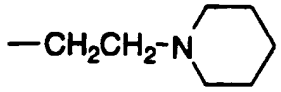
N-(2-Hydroxyethyl)-29,30-dihydro-20,30-oxa-nodulisporamide

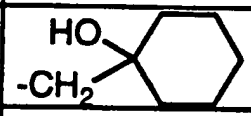
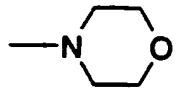
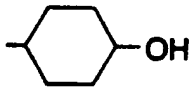
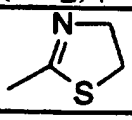
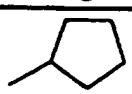
on silica gel (one 1000 micron plate) using 1/2 acetone/hexanes as eluant. Additional purification using HPLC (6/4 acetonitrile/water for 15 minutes, then a 45 minute linear gradient to 7/3 acetontrile/water) yielded pure product (17 mg). The purified product was characterized by proton NMR and MS (m/z: 735.7 (M+1)).

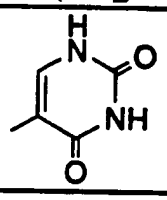
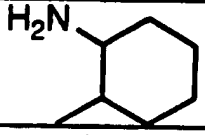
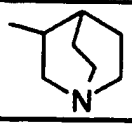
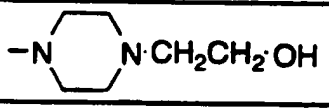
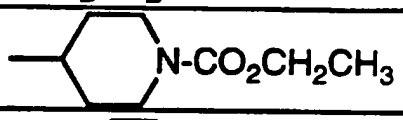
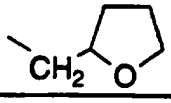
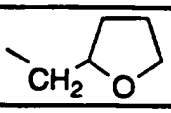
The general procedure of Example 40 was repeated using the appropriate amines listed in Table 3 below to provide the corresponding monosubstituted nodulisporamide compounds. These compounds were characterized by proton NMR and/or mass spectrometry (unless otherwise specified, m/z is for M+1).

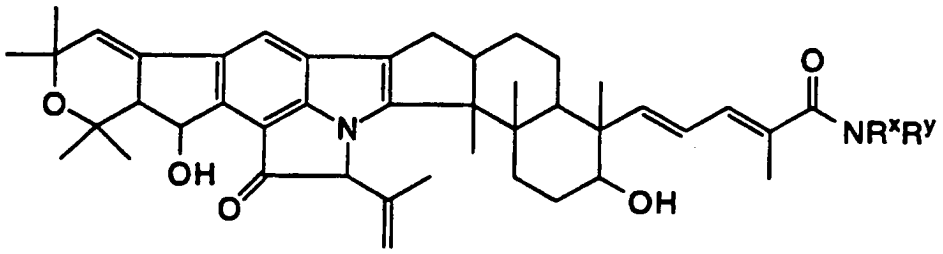
Table 3: Monosubstituted Aliphatic Nodulisporamide Derivatives

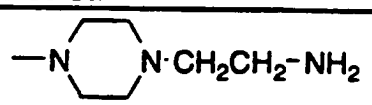
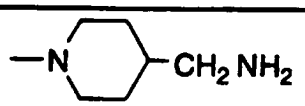
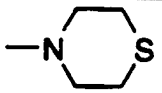
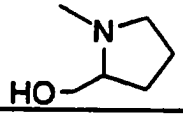
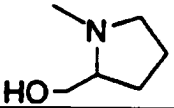
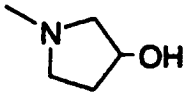
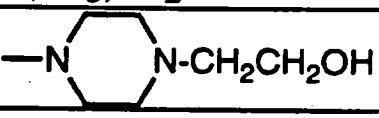
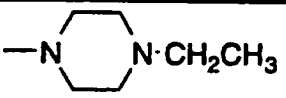


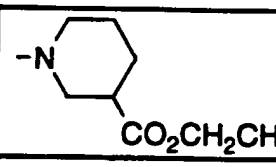
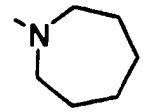
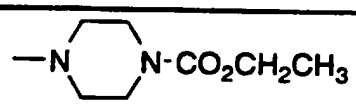
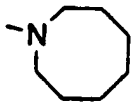
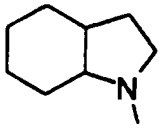
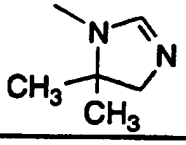
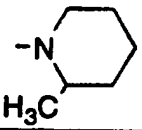
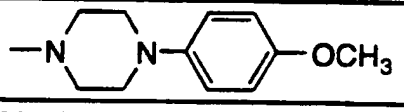
Ex.	m/z	Amines	R^x
41	796.5	Aminoacetaldehyde diethyl acetal	$CH_2CH(OCH_2CH_3)_2$
42	767.6	(2-Hydroxyethoxy)-ethylamine	$CH_2CH_2OCH_2CH_2OH$
43	792.5	4-(2-Aminoethyl)-morpholine	
44	790.4	1-(2-Aminoethyl)-piperidine	
45	807.5	6-Amino-2-methylheptan-2-ol	$CH(CH_3)(CH_2)_3C(CH_3)_2OH$
46	737.5	3-Aminopropanol	$(CH_2)_3OH$

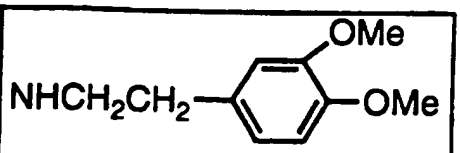
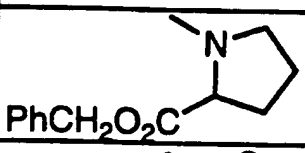
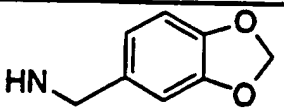
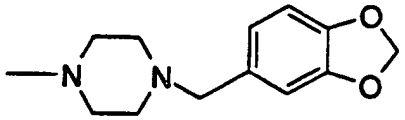
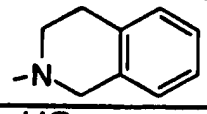
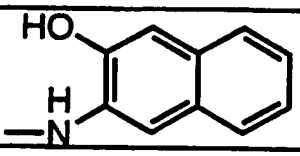
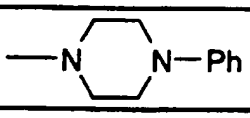
67	766.5	2-(2-Aminoethylamino)-ethanol	$CH_2CH_2NHCH_2CH_2OH$
68	791.4	1-Aminomethyl-cyclohexan-1-ol	
69	779.4	2-Aminohexanol	$CH(CH_2OH)(CH_2)_3CH_3$
70	751.5	2-Amino-1-methoxypropane	$CH(CH_2OCH_3)CH_3$
71	764.4	4-Aminomorpholine	
72	777.6	trans-4-Aminocyclohexan-1-ol	
73	739.4	2-Aminoethanethiol	$(CH_2)_2SH$
74	750.5	4-Aminobutylamine	$(CH_2)_4NH_2$
75	764.4	2-Amino-4,5-dihydrothiazole	
76	747.5	Aminocyclopentane	
77		2-(Methylsulfonyl)-ethylamine	$CH_2CH_2SO_2CH_3$
78		2-(Methylsulfinyl)-ethylamine	$CH_2CH_2S(O)CH_3$
79	765.4	2-Amino-3-methylbutanol	$CH(CH(CH_3)_2)CH_2OH$
80	736.5	3-Aminopropylamine	$(CH_2)_3NH_2$
81	792.5	3-(Diethylamino)-propylamine	$(CH_2)_3N(CH_2CH_3)_2$
82	764.5	3-(Dimethylamino)-propylamine	$(CH_2)_3N(CH_3)_2$
83	723.5	O-Ethylhydroxylamine	OCH_2CH_3
84	753.5	3-Amino-2-hydroxypropanol	$CH_2CH(OH)CH_2OH$
85	709.4	O-Methylhydroxylamine	OCH_3
86	737.4	2-Methoxyethylamine	$CH_2CH_2OCH_3$

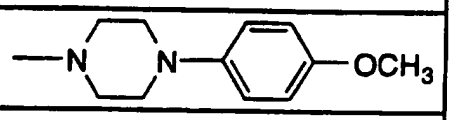
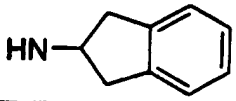
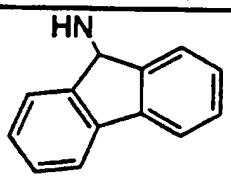
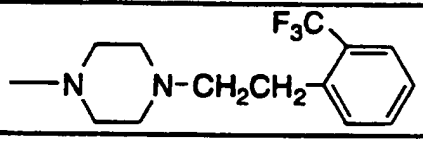
107	777.5	4-Amino-4-methyl-pentan-2-one	$C(CH_3)_2CH_2C(O)CH_3$
108	837.6	Diethyl 2-aminomalonate	$CH(CO_2CH_2CH_3)_2$
109		5-Aminouracil	
110	707.6	Ethylamine	CH_2CH_3
111	807.8	Norleucine methyl ester	$CH(CH_2CH_2CH_3)CO_2CH_3$
112	751.7	3-Methoxypropylamine	$CH_2CH_2CH_2OCH_3$
113	745.5	1,1-Dimethylpropargyl-amine	$C(CH_3)_2C{\equiv}CH$
114	749.7	Pentylamine	$(CH_2)_4CH_3$
115	777.9	4-Aminoheptane	$CH(CH_2CH_2CH_3)_2$
116	763.8	Hexylamine	$(CH_2)_5CH_3$
117	776.8	cis-1,2-Diaminocyclohexane	
118	788.9	3-Aminoquinuclidine	
119	751.7	beta-Alanine	$CH_2CH_2CO_2H$
120	793.5	L-Valine methyl ester	$CH(CH(CH_3)_2)CO_2CH_3$
121		1-Amino-4-(2-Hydroxyethyl)piperazine	
122	753.4	Aminooxyacetic acid	OCH_2CO_2H
123	834.5	4-Amino-1-carboethoxypiperidine	
124	763.5	(R)-2-(Aminomethyl)-tetrahydrofuran	
125	763.6	(S)-2-(Aminomethyl)-tetrahydrofuran	

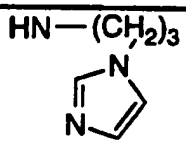
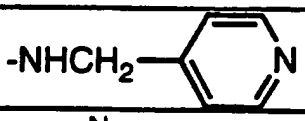
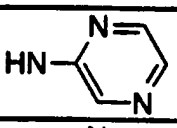
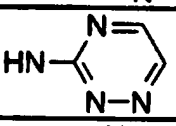
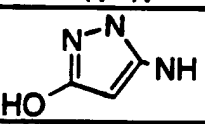
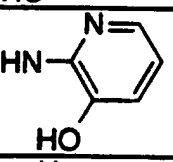
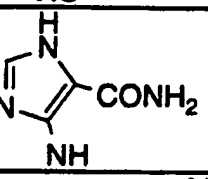
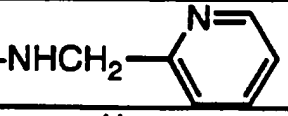
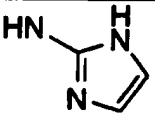
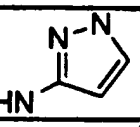
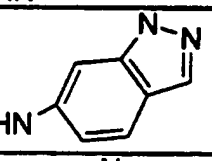
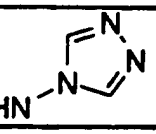


Ex.	m/z	Amine	NR^XR^Y
144	791.5	1-(2-Aminoethyl)-piperazine	
145	776.6	4-Aminomethylpiperidine	
146	765.4	Thiomorpholine	
147	759.4	Diallylamine	$N(CH_2CH=CH_2)_2$
148	737.4	2-(Methylamino)ethanol	$N(CH_3)CH_2CH_2OH$
149	795.4	Diisopropanolamine	$N(CH_2CH(CH_3)OH)_2$
150	763.5	L-2-(Hydroxymethyl)-pyrrolidine	
151	763.5	D-2-(Hydroxymethyl)-pyrrolidine	
152	749.5	3-Hydroxypyrrolidine	
153	732.7	Methylaminoacetonitrile	$N(CH_3)CH_2C{\equiv}N$
154		4-(2-hydroxyethyl)-piperazine	
155	777.7	4-Ethylpiperazine	
156	721.5	N-Ethylmethylamine	$N(CH_3)CH_2CH_3$
157	735.6	N-(Methyl)isopropylamine	$N(CH_3)CH(CH_3)_2$

175	819.6	3-(Carboethoxy)piperidine	
176	761.6	Hexamethyleneimine	
177	820.7	1-(Carboethoxy)piperazine	
178	819.7	Dipentylamine	$N(CH_2CH_2CH_2CH_2CH_3)_2$
179	775.6	Heptamethyleneimine	
180	787.6	Octahydroindole	
181	760.5	4,5-Dihydro-5,5-dimethylimidazole	
182	707.5	Dimethylamine	$N(CH_3)_2$
183	763.7	Dipropylamine	$N(CH_2CH_2CH_3)_2$
184	761.7	2-Methylpiperidine	
185	779.5	2-(Butylamino)ethanol	$N((CH_2)_2CH_3)CH_2CH_2OH$
186	731.7	Methylpropargylamine	$N(CH_3)CH_2C{\equiv}CH$
187	854.7	1-(4-Methoxyphenyl)-piperazine	
188	931.9	Dinonylamine	$N((CH_2)_8CH_3)_2$
189	903.8	Dioctylamine	$N((CH_2)_7CH_3)_2$

212	843.8	4-(2-Aminoethyl)-1,2-dimethoxybenzene	
213	867.5	L-Proline benzyl ester	
214	813.8	4-Aminomethyl-1,2-methylenedioxybenzene	
215	837.5	4-(Trifluoromethyl)-benzylamine	$NHCH_2Ph(4\text{-}CF_3)$
216	882.6	1-((3,4-methylenedioxy)-benzyl)piperazine	
217	862.7	3-(Benzyloxy)aniline	$NHPh(4\text{-}OCH_2Ph)$
218	801.4	4-(Methylthio)aniline	$NHPh(4\text{-}SCH_3)$
219	855.5	L-Phenylalanine ethyl ester	$NHCH(CH_2Ph)CO_2CH_2CH_3$
220	841.4	D-Phenylalanine methyl ester	$NHCH(CH_2Ph)CO_2CH_3$
221	799.4	4-(Methoxy)benzylamine	$NHCH_2Ph(4\text{-}OCH_3)$
222	819.5	1-(Aminomethyl)napthalene	$NHCH_2$-1-naphthyl
223	792.4	1,2,3,4-Tetrahydro-isoquinoline	
224	821.8	3-Amino-2-hydroxy-napthalene	
225	801.7	3-(2-Aminoethyl)-fluorobenzene	$NHCH_2CH_2(3\text{-}F)Ph$
226	823.7	4-Phenylpiperazine	
227	814.7	D-Phenylalaninol	$NHCH(CH_2Ph)CH_2OH$

247	812.7	N-Methyl-N-phenyl-ethylenediamine	$NHCH_2CH_2N(CH_3)Ph$
248	837.6	3-(Trifluoromethyl)-benzylamine	$NHCH_2Ph(3\text{-}CF_3)$
249	837.7	2-(Trifluoromethyl)-benzylamine	$NHCH_2Ph(2\text{-}CF_3)$
250		1-(4-Methoxyphenyl)-piperazine	
251	795.7	2-Aminoindane	
252	843.6	9-Aminofluorene	
253	811.7	4-Phenylbutylamine	$NH(CH_2)_4Ph$
254	827.8	(R,R)-2-Methylamino-3-phenylbutane	$N(CH_3)CH(CH_3)CH(CH_3)Ph$
255	827.8	(S,S)-2-Methylamino-3-phenylbutane	$N(CH_3)CH(CH_3)CH(CH_3)Ph$
256	825.9	Benzylbutylamine	$N(CH_2Ph)(CH_2)_3CH_3$
257	785.6	O-Benzylhydroxylamine	$NHOCH_2Ph$
258	805.5	2,6-Difluorobenzylamine	$NCH_2Ph(2,6\text{-}diF)$
259	920.9	1-(2-(o-Trifluoromethyl-phenyl)ethyl)piperazine	
260	797.7	(S)-N,alpha-Dimethylbenzylamine	$N(CH_3)CH(CH_3)Ph$
261	783.7	(S)-alpha-Methylbenzylamine	$NHCH(CH_3)Ph$
262	797.6	Methyl benzyl amine	$N(CH_3)CH_2Ph$
263		4-Aminomethyl-1,2-dichlorobenzene	$NHCH_2Ph(3,4\text{-}diCl)$

281	787.5	1-(3-Aminopropyl)-imidazole	
282	770.6	4-(Aminomethyl)pyridine	
283	757.4	2-Aminopyrazine	
284		3-Amino-1,2,4-triazine	
285		5-Amino-3-hydroxypyrazole	
286		2-Amino-3-hydroxypyridine	
287		4-Amino-5-carboxamidoimidazole	
288	770.4	2-(Aminomethyl)pyridine	
289	751.5 M+Li	2-Aminoimidazole	
290	745.4	3-Aminopyrazole	
291	795.2	6-Aminobenzopyrazole	
292	797.5	4-Amino-1,2,4-triazole	

General Procedure for the Preparation of Additional Amide Derivatives of Nodulisporic Acid

To a solution of 30 mg of nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of amine selected from Table 5. Stir the solution overnight at 4 °C and then pour into 1/1 saturated sodium bicarbonate/brine, extract with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution to dryness under reduced pressure. Pure product may be obtained by flash chromatography or preparative TLC on silica gel or reversed-phase liquid chromatography. The purified product may be characterized by proton NMR and mass spectrometry.

Table 5: Amines for the Preparation of Additional Nodulisporamide Derivatives

N-Methyl-2,2,2-trifluoroethylamine, 2,2,3,3,3-Pentafluoropropylamine, N-Methyl-2,2,3,3,3-pentafluoropropylamine, 1,1,1,3,3,3-Hexafluoroisopropylamine , 2-Difluoro-3-Methoxy-1-methyl-propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine , 1,1,1-Trifluoromethylpropylamine, 2-(3,3,3-Trifluoromethyl)propylamine, N-Methyl-1,1,1,3,3,3-hexafluoroisopropylamine , Di-(2,2,2-trifluoroethyl)amine, N-(2-Methoxyethyl)-2,2,2-trifluoroethylamine, 2-Methoxy-1-methyl-ethylamine, 3-Methoxy-1-methyl-propylamine, 2-Methoxy-1-methyl-ethylamine, N-Methyl-2-methoxy-1-benzyl-ethylamine, 1-Methoxymethyl-3-methyl-butylamine, Methylsulfonamide, Isopropylsulfonamide, Ethylsulfonamide, Benzylsulfonamide, sec-Butylsulfonamide, N-Methyl-ethylsulfonamide, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine, 1-Methyl-propargylamine, 1-Trifluoromethylpropargylamine, N,1,1-Trimethyl-propargylamine, N-Ethyl-1,1-dimethyl-propargylamine, N,1-Dimethyl-propargylamine,

phenethylamine, 4-(2-Methoxyethyl)phenethylamine, 4-(Ethoxymethyl)phenethylamine, 4-(Acetoxyoxymethyl)phenethylamine, 3-(Dimethylaminomethyl)phenethylamine, 1-Phenyl-2,2,2-trifluoroethylamine, 4-(Trifluoromethoxy)aniline, 4-Methoxyaniline, 4-Ethoxyaniline, 3-Chloro-4-fluoro-aniline, 4-Chloro-2-fluoro-aniline, 4-(Acetoxy)aniline, 4-(Butoxy)aniline, 3-Chloroaniline, 4-(Methylthio)aniline, 5-(Aminomethyl)benzofuran, 5-(Methylaminomethyl)benzofuran, 4-(1-Aminoethyl)benzofuran, 5-(2-Aminoethyl)benzofuran, 5-Aminomethyl-2,3-dihydro-benzofuran, 5-Methylaminomethyl-2,3-dihydro-benzofuran, 4-1-Aminoethyl-2,3-dihydro-benzofuran, 5-2-Aminoethyl-2,3-dihydro-benzofuran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-1-Aminoethyl-2H-tetrahydrobenzopyran, 5-2-Aminoethyl-2H-tetrahydrobenzopyran, 5-Aminomethyl-2H-tetrahydrobenzopyran, 5-Methylaminomethyl-2H-tetrahydrobenzopyran, 4-(1-Aminoethyl)-2H-tetrahydrobenzopyran, 5-(2-Aminoethyl)-2H-tetrahydrobenzopyran, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-1-Aminoethyl-benzo-1,4-dioxane, 5-2-Aminoethyl-benzo-1,4-dioxane, 5-Aminomethyl-benzo-1,4-dioxane, 5-Methylaminomethyl-benzo-1,4-dioxane, 4-(1-Aminoethyl)-benzo-1,4-dioxane, 5-(2-Aminoethyl)-benzo-1,4-dioxane, 3-Amino-5-methoxy-thiophene, 2-Amino-5-chloro-thiophene, 2-(2-Aminoethyl)thiophene, 2-(3-Aminopropyl)thiophene, 3-(3-Aminopropyl)thiophene, 3-(2-Methylaminoethyl)thiophene, 2-Chloro-3-(2-aminoethyl)-thiophene, 2-Aminoethyl-4-methoxy-thiophene, 2-Amino-3-ethyl-thiophene, 2-(Methylaminomethyl)thiophene, 3-(Aminomethyl)thiophene, 2-(2-Aminoethyl)-4-methoxy-thiophene, 1-(Aminomethyl)tetrazole, 1-(1-Aminoethyl)tetrazole, 1-(3-Aminopropyl)tetrazole, 5-Amino-3-methyl-isoxazole, 3-Aminopyridine, 4-Aminomethylthiazole, 2-(2-Aminoethyl)pyrazine, 2-(1-Aminoethyl)imidazole, 2-(Aminomethyl)isoxazole, 3-(2-Aminoethyl)pyrazole, 2-(Aminomethyl)-1,3,4-thiadiazole.

EXAMPLE 304

2-(Methanesulfinyl)ethylamine, 4-(2-Hydroxyethyl)aniline, 2-(2-Hydroxyethyl)aniline, 2-Amino-3-methylbutanol, Diallylamine, 2-(Methylamino)ethanol, O-Ethylhydroxylamine, 3-Amino-2-hydroxypropanol, O-Methylhydroxylamine, L-(Hydroxymethyl)pyrolidine, 2-Methoxyethylamine, N-Acetylethylenediamine, D-(Hydroxymethyl)pyrrolidine, 3-Hydroxypyrolidine, 2-(Aminoethyl)benzene, 2-Amino-2-methyl-propanol, Cyclohexylamine, 3-Ethoxypropylamine, Allylamine, 2-Amino-2-hydroxymethyl-butanol, Propargylamine, 2-Fluoroethylamine, 3-(Dimethylamino)aniline, 2-Dimethylaminoethanol, 4-(2-hydroxyethyl)piperazine, 4-Ethylpiperazine, N-Ethylmethylamine, N-(Methyl)isopropylamine, 2,2,2-Trifluoroethylamine, N-Methylpropylamine, N-Methylbutylamine, N-Ethyl-2-methoxyethylamine, 4-(Aminoethyl)phenol, N-Methyl-2-methoxyethylamine, N-Ethylpropylamine, D,L-2-(Aminomethyl)tetrahydrofuran, 1-Aminopiperidine, D-Alanine methyl ester, 3,5-Diamino-1,2,4-triazole, Benzylsulfonamide, 4-Amino-4-methyl-pentan-2-one, 5-Aminouracil, Ethylamine, Norleucine methyl ester, 3-Methoxypropylamine, 3-Hydroxypiperidine, 4-Hydroxypiperidine, 1,1-Dimethylpropargylamine, N-(Ethyl)isopropylamine, Pentylamine, Piperidine, 2-Fluorophenylhydrazine, Hexylamine, Diethylamine, 4-(2-Aminoethyl)-1,2-dimethoxybenzene, 1-(2-Pyridyl)piperazine, 4-Methylpiperazine, 4-(2-Hydroxyethyl)morpholine, 4-Aminomethyl-1,2-methylenedioxybenzene, 1-((3,4-methylenedioxy)benzyl)piperazine, 4-(Ethylaminomethyl)pyridine, L-Valine methyl ester, D-Phenylalanine methyl ester, 4-(Methoxy)benzylamine, 1-Amino-4-(2-hydroxyethyl)piperazine, 1,2,3,6-Tetrahydropyridine, 3-(2-Aminoethyl)fluorobenzene, 1-Phenylpiperazine, 4-Amino-1-carboethoxypiperidine, 1-(Carboethoxy)piperazine, (R)-2-(Aminomethyl)tetrahydrofuran, (S)-2-(Aminomethyl)tetrahydrofuran, L-Valinol, D-Valinol, L-Alaninol, D-Phenylalaninol, 3,4-Dihydroxytetrahydrofuran, D-Alaninol, 2-Fluorobenzylamine, 4-Fluoroaniline, Isopropylamine, tert-Butylamine, iso-Butylamine, 4-(2-

Trifluoromethylamino-4-pentyne, N-(2-Methoxyethyl)-2-amino-1,1-dimethyl-2-butyne, 1-Amino-2-butyne, 1-Amino-3-butyne, N-Methylamino-2-butyne, N-Methylamino-3-butyne, 1-Ethylamino-3-butyne, 2-(Aminomethyl)dioxane, 2-(2-Aminoethyl)dioxane, 2-(3-Aminopropyl)dioxane, 2-(2-Aminopropyl)dioxane, 2-(Methylaminomethyl)dioxane, 2-(1-Aminoethyl)dioxane, 2-Aminomethyl-2H-tetrahydropyran, 2-(2-Aminoethyl)-2H-tetrahydropyran, 2-(3-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)-2H-tetrahydropyran, 2-(2-Aminoethyl)-5-ethyl-2H-tetrahydropyran, 2-Methylaminomethyl-2H-tetrahydropyran, 2-(1-Aminoethyl)-2H-tetrahydropyran, 2-(2-Aminopropyl)tetrahydrofuran, 2-Aminomethyl-5-ethyl-tetrahydrofuran, 2-Methylaminomethyl-tetrahydrofuran, 2-(Ethylaminomethyl)tetrahydrofuran, 2-(1-Aminoethyl)tetrahydrofuran, 4-(Methoxymethyl)benzylamine, 4-(2-Methoxyethyl)benzylamine, 4-(Ethoxymethyl)benzylamine, 4-(Acetoxyoxymethyl)benzylamine, 3-(Dimethylaminomethyl)benzylamine, 4-(Sulfonamidomethyl)benzylamine, 2-Chloro-6-fluoro-benzylamine, 3-Chloro-4-fluoro-benzylamine, 2-Chloro-4-fluoro-benzylamine, 3,5-Difluoro-benzylamine, 2,4-Difluoro-benzylamine, Pentafluorobenzylamine, 4-Methoxy-2,3,5,6-tetrafluorobenzylamine, 4-(Methyl)benzylamine, Benzylamine, 4-(Ethyl)benzylamine, 4-(Ethoxy)benzylamine, 4-(Isopropyl)benzylamine, 4-(Isobutyl)benzylamine, 4-(Isopropropoxy)benzylamine, 4-(Isobutoxy)benzylamine, 4-(Allyl)benzylamine, 4-(Allyloxy)benzylamine, 4-(3,3,1,1-Tetrafluoroallyloxy)benzylamine, 4-(Trifluoromethoxy)benzylamine, 4-(2,2,2-trifluoroethoxy)benzylamine, 3,4-Ethylenedioxybenzylamine, 4-Methoxymethyl-2-chloro-phenethylamine, 4-(2-Methoxyethyl)phenethylamine, 4-(Ethoxymethyl)phenethylamine, 4-(Acetoxyoxymethyl)phenethylamine, 3-(Dimethylaminomethyl)phenethylamine, 1-Phenyl-2,2,2-trifluoroethylamine, 4-(Trifluoromethoxy)aniline, 4-Methoxyaniline, 4-Ethoxyaniline, 3-Chloro-4-fluoro-aniline, 4-Chloro-2-fluoro-aniline, 4-(Acetoxy)aniline, 4-(Butoxy)aniline, 3-Chloroaniline, 4-

room temperature, extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purified product was obtained following preparative TLC (1 x 0.5 mm silica gel) using 6:4 EtOAc/hexanes as eluant. The purified product was characterized by ^1H NMR.

EXAMPLE 306

N-(2-Tetrahydrofuranylmethyl)-29,30,31,32-tetrahydro-nodulisporamide

To 40 mg N-(2-tetrahydrofuranylmethyl)-nodulisporamide in 2 mL methanol at room temperature was added 20 mg 10% Pd on carbon. One atmosphere of hydrogen was established and maintained for 2 hours using a balloon. After removal of the catalyst by filtration through Celite using methanol as eluant, the solution was concentrated under reduced pressure and 3 mg pure product was obtained following preparative TLC on silica gel (two 1000 micron plates). The product was characterized by NMR and mass spectrometry (m/z: 767 (M +1)).

EXAMPLE 307

N-Ethyl-N-methyl-29,30,31,32-tetrahydro-nodulisporamide

To 23 mg of N-ethyl-N-methyl-nodulisporamide in 2 mL methanol at room temperature was added 40 mg 10% Pd on carbon. One atmosphere of hydrogen was established and maintained for 3 hours using a balloon. After removal of the catalyst by filtration through Celite using methanol as eluant, the solution was concentrated under reduced pressure and 9.5 mg of reduced product was obtained following medium pressure liquid chromatography (93/7 methanol/water as eluant). The product was characterized by proton NMR and mass spectrometry (m/z: 723 (M+1)).

EXAMPLE 308

General Procedure for the Preparation of
29,30,31,32-Tetrahydro-nodulisporic Acid Derivatives

EXAMPLE 311
General Procedure for the Preparation of 29,30-Dihydro-Nodulisporic Acid Derivatives

To a solution of 30 mg of 29,30-dihydro-nodulisporic acid in 3 mL methylene chloride at 0 °C add 0.03 mL triethylamine and 12 mg N-hydroxybenzotriazole followed by 28 mg BOP reagent. Stir the solution for 10 minutes and then add 50 mg of an amine or an alcohol selected from Table 6. Stir overnight at 4 °C and then at room temperature for 2 hours. Pour the solution into 1/1 saturated sodium bicarbonate/brine. Extract the solution with methylene chloride and dry the combined organic layers over sodium sulfate. Remove the solids by filtration and concentrate the solution under reduced pressure. Pure product may be obtained following purification by flash chromatography, preparative TLC or reversed-phase liquid chromatography. Products may be characterized by proton NMR and or mass spectrometry.

EXAMPLE 312
General Procedure for the Preparation of 31,32-Dihydro-Compound B Derivatives

Place 50 mg of a ester or amide analog prepared from compound B and the amines listed in Table 6 or alcohols listed in Table 2 in 4 mL methanol at room temperature. Hydrogenation of the 31,32-double bond may be accomplished using 10% Pd on carbon under 1 atmosphere of hydrogen from 15 minutes to 24 hours. The catalyst may be removed by filtration through a pad of Celite using methanol as eluant. Concentration of the solution under reduced pressure followed by purification on silica gel by either flash chromatography, preparative TLC or by reversed-phase liquid chromatography will yield the desired 31,32-dihydro-Compound B derivative.

nodulisporic acid

Heat 20 mg of 29,30-dihydro-20,30-oxa-nodulisporyl azide in 8 mL toluene to 90 °C for 2 h. The solvent may be removed by evaporation and the product which is obtained may be characterized by proton NMR and mass spectrometry.

EXAMPLE 316

32-Descarboxy-32-isocyanato-nodulisporic acid

A solution of 54 mg of nodulisporyl azide in toluene was heated at 90°C for 2 h. The solvent was then evaporated and the isocyanate product was obtained in quantitative yield and was characterized by ^{1}H NMR and mass spectrometry.

EXAMPLE 317

32-Descarboxy-32-(1-carbomethoxyamino)-nodulisporic acid

To 1.3 mg of isocyanate of Example 313 in 1 mL of methanol was added 20 microliters of triethylamine. The reaction mixture was heated for 45 min at 75°C and the carbamate product (0.7 mg) was isolated by preparative TLC on silica gel (1 x 0.5 mm) and characterized by ^{1}H NMR and mass spectrometry.

EXAMPLE 318

32-Descarboxy-32-(1-(3-benzyl)urea)-nodulisporic acid

To 1 mg of isocyanate of Example 313 in 0.2 mL of toluene was added 40 microliters of benzylamine. The mixture was stirred at 20°C for 20 min and the urea product (0.2 mg) was isolated by preparative TLC (1 x 0.5 mm silica gel, 1:3 hexane:EtOAc) and characterized by its ^{1}H NMR and MS.

the isocyanate product thus obtained may be characterized by ^1H NMR and mass spectrometry.

EXAMPLE 339

General Procedure for the Synthesis of 29,30-Dihydro-20,30-oxa-32-descarboxy-32-[UREA]- or 29,30-Dihydro-20,30-oxa-32-descarboxy-32-[CARBAMATE]-Nodulisporic Acid Derivatives

To 1 mg of 29,30-dihydro-20,30-oxa-32-descarboxy-32-isocyanato-nodulisporic acid in 0.2 mL of toluene add 40 mg of an amine selected from Table 6 or alcohol selected from Table 2. Stir the mixture at 20°C from 20 minutes to 24 hours. Pure urea or carbamate product may be isolated by flash chromatography, preparative TLC or reversed-phase liquid chromatography. The purified products may be characterized by proton NMR and mass spectrometry.

EXAMPLE 340

31-Hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporyl azide

To 1 mg 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporic acid in 0.2 mL chloroform add 0.05 mL triethylamine followed by 0.02 mL diphenylphosphoryl azide. Stir the reaction at room temperature for 3 h before purification by flash chromatography or preparative TLC on silica gel. The product which is obtained may be characterized by proton NMR and mass spectrometry.

EXAMPLE 341

31-Hydroxy-20,30-oxa-29,30,31,32-tetrahydro-32-descarboxy-32-isocyanato-nodulisporic acid

Heat a solution of 54 mg of 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporyl azide in toluene at 90°C for 2 h.

was purified by reversed-phase HPLC without workup using 30:70 to 15:85 (25 minute linear gradient) water/methanol to yield pure product. The product was characterized by ^1H NMR.

EXAMPLE 345
N-Ethyl-N-methyl-1-hydroxy-nodulisporamide

To 30 mg N-ethyl-N-methyl-nodulisporamide in 2 mL tetrahydrofuran at room temperature was added 1 mL diisobutylaluminum hydride (1.0 M solution in hexanes). After 3 days at room temperature, the reaction was quenched by the addition of acetic acid. The solution was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography on silica gel using 1/1 acetone/hexanes as eluant. The purified product was characterized by proton NMR and mass spectrometry (m/z: 723 (M+1)).

EXAMPLE 346
1-Hydroxy-Compound B or C

To 5 mg of Compound B or C in 2 mL of methanol at 0°C under argon add 5 mg of sodium borohydride. After 10 min at 0°C, extract the products with methylene chloride. Dry the combined extracts over sodium sulfate and concentrate the solution in vacuo. The residual solid may be purified purified by flash chroimatography, preparative TLC or reversed-phase liquid chromatography to yield 1-hydroxy-Compound B or C as a mixture of stereoisomers which may be characterized by proton NMR and mass spectrometry.

EXAMPLE 347
General Procedure for Synthesis of 1-Hydroxy-Amide and Ester Derivatives of Compounds A, B and C

EXAMPLE 350

1-Hydroxy-1-Alkyl- or 1-Hydroxy-1-Aryl-Compounds A, B or C

To 0.5 mL solution of 1.0 M Grignard reagent selected from Table 8 in 1/1 THF/toluene at 0°C add 1 mg Compound A, B or C dissolved in 0.6 mL THF. After 10 min at 0°C, quench the reaction with 2N HCl and extract with methylene chloride. Dry the combined organic layers over sodium sulfate, filter and concentrate under reduced pressure. Pure product may be obtained following flash chromatography, preparative TLC or reversed-phase liquid chromatography. Purified products may be characterized by proton NMR or mass spectrometry.

Table 8: Grignard Reagents

Methyl magnesium bromide
Ethyl magnesium chloride
iso-Propyl magnesium bromide
Phenyl magnesium iodide
Benzyl magnesium bromide
Allyl magnesium bromide
Propargyl magnesium bromide
Magnesium bromide acetilide

EXAMPLE 351

1-Hydroxy-32-descarboxy-32-hydroxymethyl-nodulisporic acid

To 1.2 mg methyl nodulisporate in 1.2 mL tetrahydrofuran at -78°C was added 20 µL 1M lithium aluminum hydride in tetrahydrofuran. The yellow color rapidly disappeared. After 10 minutes, the reaction was quenched at -78°C by dropwise addition of saturated Na_2SO_4. The solution was extracted with ethyl acetate, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Pure product was obtained following preparative TLC (1 x 0.25 mm silica gel

EXAMPLE 354
4,20-bis-O-Acetyl-nodulisporic acid

To 1.2 mg of nodulisporic acid was added 300 microliters of acetic anhydride and 100 microliters of pyridine. The reaction mixture was heated at 65°C for 1 h and excess solvent was removed in vacuo. The residual solid was purified by preparative TLC on silica gel eluted with 95:5 dichloromethane:methanol to yield 1.2 mg of the bis-acetate characterized by its ^{1}H NMR.

EXAMPLE 355
N-Ethyl-N-methyl-20-dimethylaminocarbonyloxy-nodulisporamide

To 30 mg N-ethyl-N-methyl-nodulisporamide in 3 mL methylene chloride at 4 °C was added 60 mg carbonyldiimidazole. After 3 days at 4 °C, 1 mL dimethylamine (25% in water) was added and the solution stirred for an additional 4 days. The solution was poured into brine, extracted with methylene chloride, dried with sodium sulfate and evaporated to dryness. Product was partially purified by flash chromatography on silica gel using 4/6 acetone/hexanes as eluant. Additional purification using medium pressure liquid chromatography (92/8 methanol/water as eluant) yielded 18 mg pure product. The purified product was characterized by proton NMR and mass spectrometry (m/z: 792 (M+1)).

EXAMPLE 356
N-Ethyl-N-methyl-1-desoxo-1-methoximino-nodulisporamide

To a solution of 30 mg N-ethyl-N-methyl-nodulisporamide and 30 mg methoxylamine hydrochloride in 4 mL ethanol was added 0.1 mL pyridine. The solution was heated to reflux for 2 days, cooled to room temperature and concentrated under reduced pressure. The residue was diluted with methylene chloride, washed with brine, dried over sodium

Similarly, amide and ester derivatives of compounds A, B and C, prepared using the amines listed in Table 6 and alcohols in Table 2, may be substituted for compounds A, B and C in the above procedure.

Table 9: Oxime Reagents

Hydroxylamine
O-Methylhydroxylamine
O-Ethylhydroxylamine
O-Benzylhydroxylamine
O-tert-Butylhydroxylamine
O-(Pentafluorobenyzl)hydroxylamine
O-Allylhydroxylamine
O-Phenylhydroxylamine
O-iso-Butylhydroxylamine
O-(2-Chloro-6-fluoro-benzyl)hydroxylamine
O-(4-Methoxybenzyl)hydroxylamine

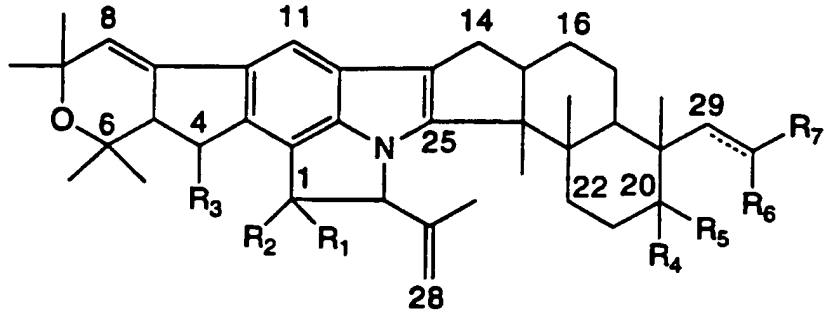
EXAMPLE 359

General Procedure for the Preparation of Hydrazinyl Derivatives of Compounds A, B and C

To a solution of 20 mg of compound A, B or C and 20 mg hydrazine selected from Table 10 in 2 mL ethanol at room temperature, add 0.02 mL pyridine. Heat the solution to reflux for 15 minutes to 24 hours, then cool to room temperature and dilute with methylene chloride. The solution may be washed with brine, the organic layer dried over sodium sulfate and concentrated to under reduced pressure. Pure product may be obtained following purification by flash chromatgraphy or preparative TLC on silica gel or reversed-phase liquid chromatography as a mixture of E- and Z-oxime isomers. The purified products may be characterized by proton NMR and mass spectrometry. Similarly, amide and ester derivatives of compounds A, B and C, prepared using the

WHAT IS CLAIMED IS:

1. A compound having the formula I:



I

wherein

R_1 is

(1) hydrogen,

(2) optionally substituted C_1-C_{10} alkyl,

(3) optionally substituted C_2-C_{10} alkenyl,

(4) optionally substituted C_2-C_{10} alkynyl,

(5) optionally substituted C_3-C_8 cycloalkyl,

(6) optionally substituted C_5-C_8 cycloalkenyl

where the substitutents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from

(i) C_1-C_5 alkyl,

(ii) X-C_1-C_{10} alkyl, where X is O or $S(O)_m$.

(iii) C_3-C_8 cycloalkyl,

(iv) hydroxy,

(v) halogen,

(vi) cyano,

(vii) carboxy,

(viii) NY^1Y^2, where Y^1 and Y^2 are independently hydrogen or C_1-C_{10} alkyl,

(ix) C_1-C_{10} alkanoylamino, and

(8) $CH_2OCO_2R^b$,
(9) $CH_2OC(O)NR^cR^d$,
(10) $C(O)NR^cNR^cR^d$, or
(11) $C(O)NR^cSO_2R^b$;

---- represents a single or a double bond;

R^a is (1) hydrogen,
(2) optionally substituted C_1-C_{10} alkyl,
(3) optionally substituted C_3-C_{10} alkenyl,
(4) optionally substituted C_3-C_{10} alkynyl,
(5) optionally substituted C_1-C_{10} alkanoyl,
(6) optionally substituted C_3-C_{10} alkenoyl,
(7) optionally substituted C_3-C_{10} alkynoyl,
(8) optionally substituted aroyl,
(9) optionally substituted aryl,
(10) optionally substituted C_3-C_7 cycloalkanoyl,
(11) optionally substituted C_5-C_7 cycloalkenoyl,
(12) optionally substituted C_1-C_{10} alkylsulfonyl
(13) optionally substituted C_3-C_8 cycloalkyl
(14) optionally substituted C_5-C_8 cycloalkenyl

where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl, cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl are from 1 to 10 groups independently selected from hydroxy, C_1-C_6 alkoxy, C_3-C_7 cycloalkyl, aryl C_1-C_3 alkoxy, NR^gR^h, CO_2R^b, $CONR^cR^d$ and halogen,

(15) C_1-C_5 perfluoroalkyl,

(16) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from C_1-C_5 alkyl, C_1-C_5 perfluoroalkyl, nitro, halogen and cyano,

(17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from C_1-C_5 alkyl, C_1-C_5 alkenyl, C_1-C_5

(xix) formyl,
(xx) -NRgRh,
(xxi) 5 to 9-membered heterocycle, which may be saturated or partially unsaturated, containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen, and optionally substituted with 1 to 5 groups independently selected from Re,
(xxii) optionally substituted aryl, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from Re,
(xxiii) optionally substituted aryl C1-C3 alkoxy, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from Re, and
(xxiv) C1-C5 perfluoroalkyl;

Rc and Rd are independently selected from Rb; or

Rc and Rd together with the N to which they are attached form a 3- to 10-membered ring containing 0 to 2 additional heteroatoms selected from O, S(O)m, and N, optionally substituted with 1 to 3 groups independently selected from Rg, hydroxy, thioxo and oxo;

Re is
(1) halogen,
(2) C1-C7 alkyl,
(3) C1-C3 perfluoroalkyl,
(4) -S(O)mRi,
(5) cyano,
(6) nitro,
(7) RiO(CH2)v-,
(8) RiCO2(CH2)v-,
(9) RiOCO(CH2)v,
(10) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C1-C6 alkyl, C1-C6 alkoxy, or hydroxy,
(11) SO2NRgRh, or
(12) amino;

(4) optionally substituted aryl C_0-C_6 alkyl, where the aryl substituents are from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and hydroxy;

m is 0 to 2; and

v is 0 to 3; or

a pharmaceutically acceptable salt thereof; and

excluding nodulisporic acid, 29,30-dihydro-20,30-oxa-nodulisporic acid, and 31-hydroxy-20,30-oxa-29,30,31,32-tetrahydro-nodulisporic acid.

2. A compound of Claim 1

wherein

R_1 is

(1) hydrogen,

(2) optionally substituted C_1-C_6 alkyl,

(3) optionally substituted C_2-C_6 alkenyl,

(4) optionally substituted C_2-C_6 alkynyl,

(5) optionally substituted C_5-C_6 cycloalkyl,

(6) optionally substituted C_5-C_6 cycloalkenyl

where the substitutents on the alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are 1 to 3 groups independently selected from

(i) C_1-C_3 alkyl,

(ii) X-C_1-C_6 alkyl, where X is O or $S(O)_m$,

(iii) C_5-C_6 cycloalkyl,

(iv) hydroxy,

(v) halogen,

(vi) cyano,

(vii) carboxy, and

(viii) NY^1Y^2, where Y^1 and Y^2 are independently hydrogen or C_1-C_6 alkyl,

(7) aryl C_0-C_3 alkyl wherein said aryl is optionally substituted with 1 to 3 groups independently selected from R^f,

(14) optionally substituted C_5-C_6 cycloalkenyl where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, alkenoyl, alkynoyl, aroyl, aryl, cycloalkanoyl, cycloalkenoyl, alkylsulfonyl, cycloalkyl and cycloalkenyl are from 1 to 10 groups independently selected from hydroxy, C_1-C_4 alkoxy, C_5-C_6 cycloalkyl, aryl C_1-C_3 alkoxy, NR^gR^h, CO_2R^b, $CONR^cR^d$ and halogen,

(15) C_1-C_3 perfluoroalkyl,

(16) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from C_1-C_3 alkyl, C_1-C_3 perfluoroalkyl, halogen and cyano,

(17) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from C_1-C_3 alkyl, C_1-C_3 alkenyl, C_1-C_3 perfluoroalkyl, amino, $C(O)NR^cR^d$, cyano, CO_2R^b and halogen, and which may be saturated or partly unsaturated;

R^b is (1) hydrogen,

(2) optionally substituted aryl,

(3) optionally substituted C_1-C_7 alkyl,

(4) optionally substituted C_3-C_7 alkenyl,

(5) optionally substituted C_3-C_7 alkynyl,

(6) optionally substituted C_5-C_7 cycloalkyl,

(7) optionally substituted C_5-C_7 cycloalkenyl, or

(8) optionally substituted 5- to 10-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen; where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from

(i) hydroxy,

(ii) C_1-C_3 alkyl,

(iii) oxo,

(iv) $SO_2NR^gR^h$,

(8) $R^iCO_2(CH_2)_v$-,
(9) $R^iOCO(CH_2)_v$,
(10) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, or hydroxy, or
(11) $SO_2NR^gR^h$;

R^f is (1) methyl,
(2) X-C_1-C_2 alkyl, where X is O or $S(O)_m$,
(3) halogen,
(4) acetylamino,
(5) trifluoromethyl,
(6) NY^1Y^2, where Y^1 and Y^2 are independently H or methyl, and
(7) hydroxy;

R^g and R^h are independently
(1) hydrogen,
(2) C_1-C_6 alkyl optionally substituted with hydroxy , amino, or CO_2R^i
(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7 alkoxy, C_1-C_7 alkyl or C_1-C_3 perfluoroalkyl,
(4) aryl C_1-C_6 alkyl, wherein the aryl is optionally substituted with C1-C3 perfluorolkyl or 1,2-methylenedioxy;
(5) C_1-C_5 alkoxycarbonyl,
(6) C_1-C_5 alkanoyl,
(7) C_1-C_5 alkanoyl C_1-C_6 alkyl,
(9) aryl C_1-C_5 alkoxycarbonyl,
(10) aminocarbonyl,
(11) C_1-C_5 monoalkylaminocarbonyl
(12) C_1-C_5 dialkylaminocarbonyl; or

R^g and R^h together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, $S(O)_m$, and N, optionally substituted with 1 to 3 groups independently selected from R^e and oxo;

(6) CH_2OR^a,
(7) $CH_2OCO_2R^b$,
(8) $CH_2OC(O)NR^cR^d$,
(9) $C(O)NR^cNR^cR^d$, or
(10) $C(O)NR^cSO_2R^b$;

R^a is (1) hydrogen,
(2) optionally substituted C_1-C_4 alkyl,
(3) optionally substituted C_3-C_4 alkenyl,
(4) optionally substituted C_3-C_4 alkynyl,
(5) optionally substituted C_1-C_4 alkanoyl,
(6) optionally substituted aroyl,
(7) optionally substituted C_5-C_6 cycloalkanoyl,
(8) optionally substituted C_5-C_6 cycloalkenoyl,
(9) optionally substituted C_1-C_3 alkylsulfonyl
where the substituents on the alkyl, alkenyl, alkynyl, alkanoyl, aroyl, cycloalkanoyl, cycloalkenoyl, and alkylsulfonyl, are from 1 to 5 groups independently selected from hydroxy, C_1-C_2 alkoxy, aryl C_1-C_3 alkoxy, NR^gR^h, CO_2R^b, $CONR^cR^d$ and halogen,
(10) trifluoromethyl,
(11) arylsulfonyl optionally substituted with 1 to 3 groups independently selected from methyl, trifluoromethyl and halogen,
(12) a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms selected from oxygen, sulfur and nitrogen optionally substituted by 1 to 4 groups independently selected from methyl, trifluoromethyl, $C(O)NR^cR^d$, CO_2R^b and halogen, and which may be saturated or partly unsaturated;

R^b is (1) hydrogen,
(2) optionally substituted aryl,
(3) optionally substituted C_1-C_6 alkyl,
(4) optionally substituted C_3-C_6 alkenyl,
(5) optionally substituted C_3-C_6 alkynyl,

(xx) optionally substituted aryl, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R^e,

(xxi) optionally substituted aryl C_1-C_3 alkoxy, wherein the aryl substituents are 1,2-methylenedioxy or 1 to 5 groups independently selected from R^e, and

(xxii) C_1-C_3 perfluoroalkyl;

R^e is

(1) halogen,

(2) C_1-C_3 alkyl,

(3) C_1-C_3 perfluoroalkyl,

(4) $-S(O)_mR^i$,

(5) cyano,

(6) $R^iO(CH_2)_v$-,

(7) $R^iCO_2(CH_2)_v$-,

(8) $R^iOCO(CH_2)_v$,

(9) optionally substituted aryl where the substituents are from 1 to 3 of halogen, C_1-C_3 alkyl, C_1-C_3 alkoxy, or hydroxy,

(10) $SO_2NR^gR^h$, or

(11) amino;

R^f is

(1) methyl,

(2) X-C_1-C_2 alkyl, where X is O or $S(O)_m$,

(3) trifluoromethyl,

(4) NY^1Y^2, where Y^1 and Y^2 are independently H or methyl,

(5) hydroxy,

(6) halogen, and

(7) acetylamino,

R^g and R^h are independently

(1) hydrogen,

(2) C_1-C_6 alkyl optionally substituted with hydroxy , amino, or CO_2R^i

(2) $C(O)N(OR^b)R^c$,
(3) $C(O)NR^cR^d$,
(4) $C(O)NR^cNR^cR^d$, or
(5) $C(O)NR^cSO_2R^b$

R_8, R_9, R^b, R^c and R^d are as defined in Claim 1.

6. A compound of Claim 5 wherein
R_{10} is $C(O)OR^b$;
R^b is
(1) optionally substituted aryl,
(2) optionally substituted C_1-C_6 alkyl,
(3) optionally substituted C_3-C_6 alkenyl,
(4) optionally substituted C_3-C_6 alkynyl,
(5) optionally substituted C_3-C_6 cycloalkyl, or
(6) optionally substituted 5 to 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;
where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from
(i) hydroxy,
(ii) C_1-C_3 alkyl,
(iii) oxo,
(iv) $SO_2NR^gR^h$,
(v) aryl C_1-C_3 alkoxy,
(vi) hydroxy C_1-C_4 alkyl,
(vii) C_1-C_4 alkoxy,
(viii) hydroxy C_1-C_4 alkoxy,
(ix) amino C_1-C_4 alkoxy,
(x) cyano,
(xi) C_1-C_4 alkyl-S(O)m,
(xii) C_5-C_6 cycloalkyl optionally substituted with 1 to 4 groups independently selected from R^e,
(xiii) C_5-C_6 cycloalkenyl,
(xiv) halogen,

selected from O, $S(O)_m$, and N, optionally substituted with 1 to 3 groups independently selected from R^e and oxo;

R^i is (1) hydrogen, or
(2) C_1-C_6 alkyl;

m is 0 to 2; and

all other variables are as defined in Claim 5.

7. A compound of Claim 5 wherein

R^{10} is (1) $C(O)N(OR^b)R^c$,
(2) $C(O)NR^cR^d$
(3) $C(O)NR^cNR^cR^d$, or
(4) $C(O)NR^cSO_2R^i$;

R^b, R^c ,R^d and R^i are as defined in Claim 5.

8. A compound of Claim 3 wherein

R^{10} is $C(O)NR^cR^d$; and

R_c and R^d are as defined in Claim 3.

9. A compound of Claim 5 wherein

R_{10} is $C(O)NR^cR^d$;

R^b is (1) hydrogen,
(2) optionally substituted aryl,
(3) optionally substituted C_1-C_6 alkyl,
(4) optionally substituted C_3-C_6 alkenyl,
(5) optionally substituted C_3-C_6 alkynyl,
(6) optionally substituted C_3-C_6 cycloalkyl,
(7) optionally substituted C_5-C_6 cycloalkenyl, or
(8) optionally substituted 5 to 6-membered heterocycle containing from 1 to 4 heteroatoms independently selected from oxygen, sulfur and nitrogen;

where the substituents on the aryl, alkyl, alkenyl, cycloalkyl, cycloalkenyl, heterocycle, or alkynyl are from 1 to 10 groups independently selected from

(i) hydroxy,

R^e is (1) halogen,
(2) C_1-C_3 alkyl,
(3) C_1-C_3 perfluoroalkyl,
(4) $R^iO(CH_2)_v$-,
(5) $R^{ji}CO_2(CH_2)_v$-,
(6) $R^iOCO(CH_2)_v$,
(7) $SO_2NR^gR^h$;
(8) amino

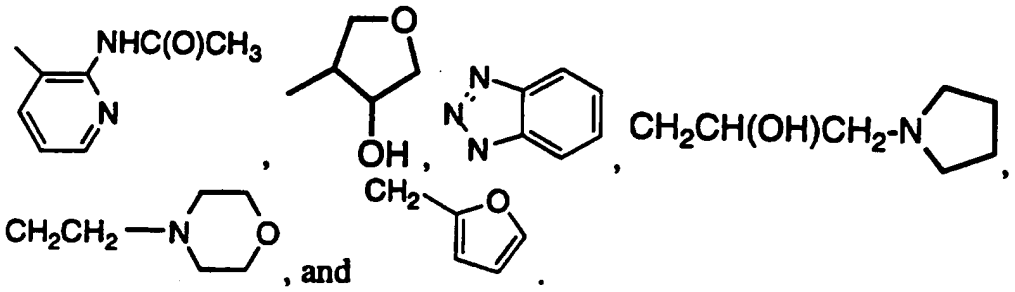
v is 0;

R^g and R^h are independently
(1) hydrogen,
(2) C_1-C_6 alkyl optionally substituted with hydroxy , amino, or CO_2R^i,
(3) aryl optionally substituted with halogen, 1,2-methylenedioxy, C_1-C_7 alkoxy, C_1-C_7 alkyl or C_1-C_3 perfluoroalkyl,
(4) aryl C_1-C_6 alkyl, wherein the aryl is optionally substituted with C_1-C_3 perfluoroalkyl or 1,2-methylenedioxy,
(5) C_1-C_5 alkoxycarbonyl,
(6) C_1-C_5 alkanoyl,
(7) aryl C_1-C_5 alkoxycarbonyl,
(8) aminocarbonyl, or

R^g and R^h together with the N to which they are attached form a 5- to 6-membered ring containing 0 to 2 additional heteroatoms selected from O, $S(O)_m$, and N, optionally substituted with 1 to 3 groups independently selected from R^e and oxo;

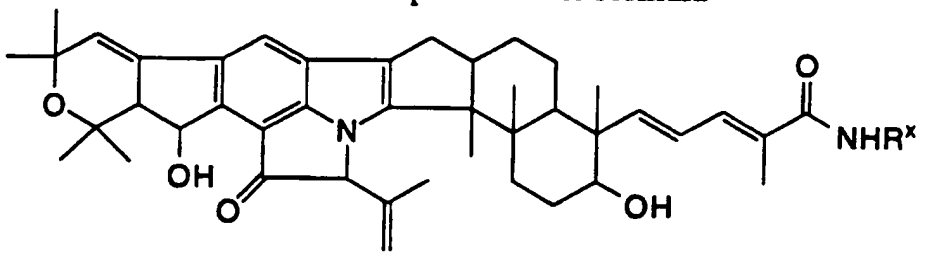
R^i is (1) hydrogen or
(2) optionally substituted C_0-C_6 alkyl wherein the substituents are aryl or substituted aryl, and the aryl substituents are from 1 to 3 groups independently selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, and hydroxy; and

all other variables are as defined in Claim 5.

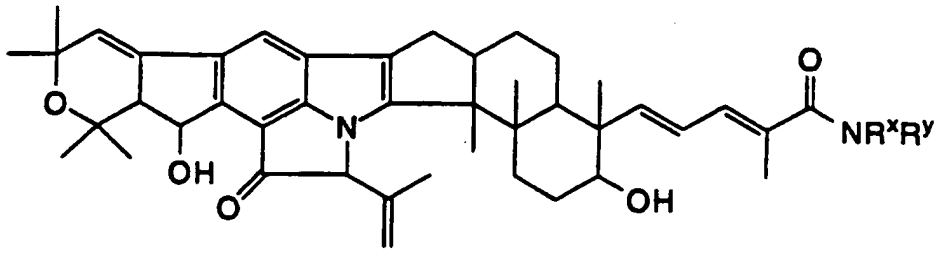


, and .

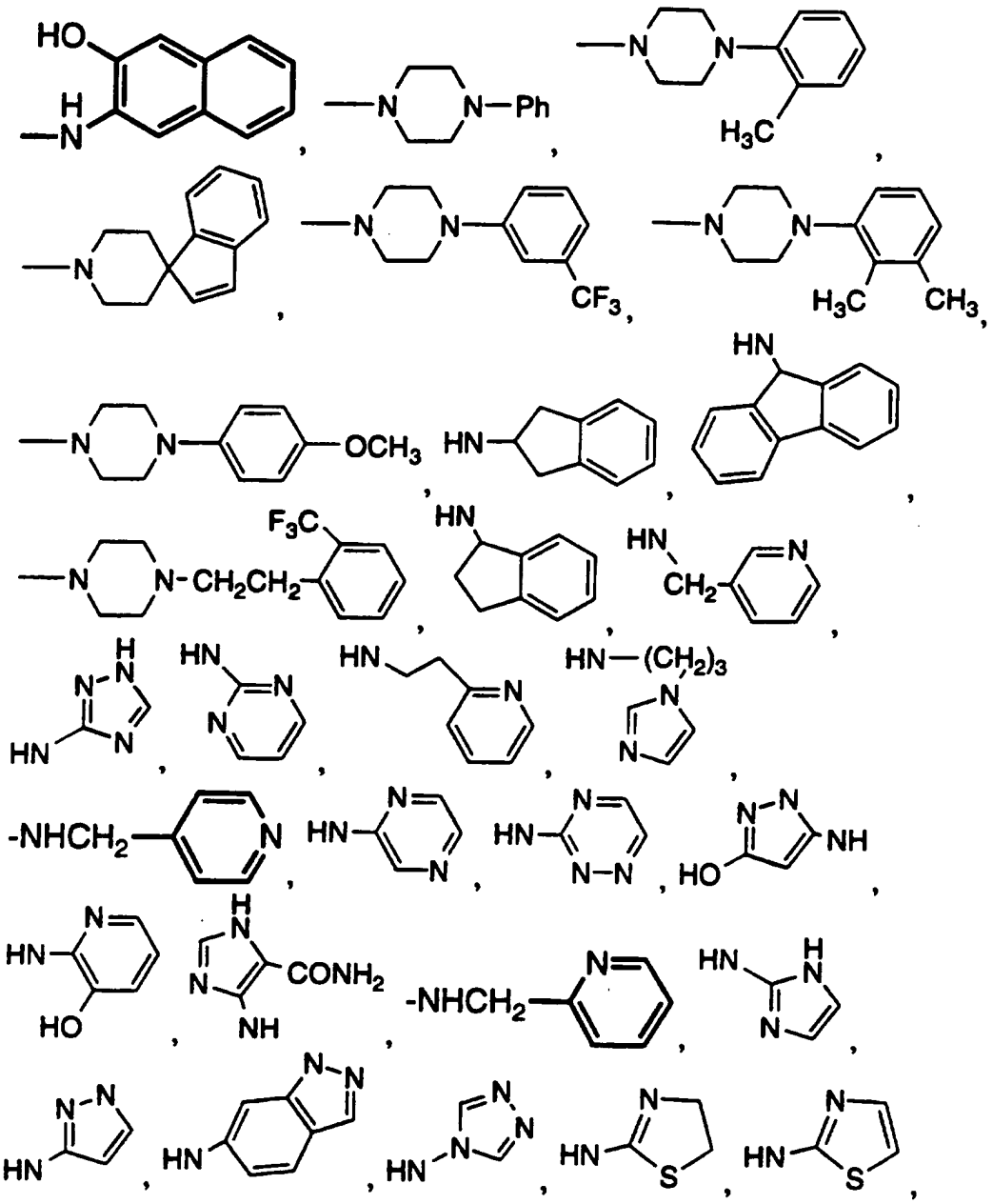
13. A compound of the formula



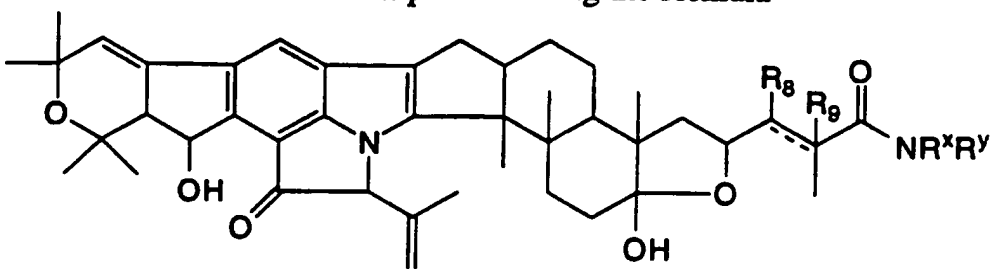
wherein R^x is selected from the group consisting of:
H, CH_3, CH_2CH_3, $C(CH_3)_3$, $CH_2CH_2CH_3$, CH_2CH_2OH, $CH(CO_2CH_3)CH_2OH$, $CH_2CO_2CH_3$, $CH_2CH(OCH_2CH_3)_2$, $CH_2CH_2OCH_2CH_2OH$, $CH(CH_3)(CH_2)_3C(CH_3)_2OH$, $(CH_2)_3OH$, $(CH_2)_4OH$, $(CH_2)_5OH$, $CH(CH_2OH)CH_2CH_3$, $NHC(CH_3)_3$, CH_2CN, $(CH_2)_6OH$, $CH_2CH(OH)CH_3$, $CH(CH_2OH)CH_2CH_2CH_3$, $CH_2CH_2SCH_3$, $CH_2CH_2SCH_2CH_3$, CH_2CONH_2, $CH(CH_3)(CH_2OH)_2$, $CH_2CH_2NHCH_2CH_2OH$, $CH(CH_2OH)(CH_2)_3CH_3$, $CH(CH_2OCH_3)CH_3$, $(CH_2)_2SH$, $(CH_2)_4NH_2$, $CH_2CH_2SO_2CH_3$, $CH_2CH_2S(O)CH_3$, $CH(CH(CH_3)_2)CH_2OH$, $(CH_2)_3NH_2$, $(CH_2)_3N(CH_2CH_3)_2$, $(CH_2)_3N(CH_3)_2$, OCH_2CH_3, $CH_2CH(OH)CH_2OH$, OCH_3, $CH_2CH_2OCH_3$, $CH_2CH_2NHC(O)CH_3$, $C(CH_3)_2CH_2OH$, c-C_3H_5, c-C_6H_{11}, $(CH_2)_3OCH_2CH_3$, $CH_2CH{=}CH_2$, $C(CH_2CH_3)(CH_2OH)_2$, $CH_2C{\equiv}CH$, $CH_2CO_2CH_2CH_3$, CH_2CH_2F, $(CH_2)_3O(CH_2)_{11}CH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2OCH_2CH_2NH_2$, CH_2CF_3, $NHCH_2CO_2CH_2CH_3$, $CH(CH_3)CO_2CH_3$, $C(CH_3)_2CH_2C(O)CH_3$, $CH(CO_2CH_2CH_3)_2$, CH_2CH_3, $CH(CH_2CH_2CH_3)CO_2CH_3$, $CH_2CH_2CH_2OCH_3$, $C(CH_3)_2C{\equiv}CH$, $(CH_2)_4CH_3$, $CH(CH_2CH_2CH_3)_2$,



wherein NR^XR^Y is selected from the group consisting of:
$N(CH_3)CH_2C{\equiv}N$, $N(CH_3)CH_2CH_3$, $N(CH_3)CH(CH_3)_2$,
$N(CH_3)CH_2CH_2CH_3$, $N(CH_3)CH_2CH_2CH_2CH_3$,
$N(CH_2CH_3)CH_2CH_2OCH_3$, $N(CH_3)CH_2CH_2OCH_3$,
$N(CH_2CH_3)CH_2CH_2CH_3$, $N(CH_2CH{=}CH_2)_2$, $N(CH_3)CH_2CH_2OH$,
$N(CH_2CH(CH_3)OH)_2$, $N(CH_2CH_3)_2$, $N(CH_2CH_2OH)_2$,
$N(CH_2CH_3)CH(CH_3)_2$, $N(CH_2CH_2CH_2CH_3)_2$,
$N(CH_2CH_2CH_2CH_2CH_3)_2$, $N(CH_3)_2$, $N(CH_2CH_2CH_3)_2$,
$N((CH_2)_2CH_3)CH_2CH_2OH$, $N(CH_3)CH_2C{\equiv}CH$, $N((CH_2)_8CH_3)_2$,
$N((CH_2)_7CH_3)_2$, $N(CH_3)(CH_2)_2NHCH_3$, $N(CH_3)(CH_2)_3NH_2$,
$NHCH(CH_2OH)CH_2Ph$, $NHPh(2\text{-}OH,4\text{-}CH_3)$, $NHCH_2Ph(4\text{-}NH_2)$,
$NHPh(4\text{-}Cl)$, $NHPh(4\text{-}CH_2CH_2OH)$, $NHPh(2\text{-}CH_2CH_2OH)$,
$NHCH_2CH_2Ph$, $NHPh(2\text{-}CH_2OH)$, $NHPh(3\text{-}N(CH_3)_2$, $NHPh(4\text{-}SO_2NH_2)$, $NHNHPh$, $NHPh(2\text{-}CONH_2)$, $NHCH_2CH_2Ph(4\text{-}OH)$,
$NHCH_2CH_2Ph(4\text{-}SO_2NH_2)$, $NHPh(2\text{-}NH_2)$,
$NHCH(CH_2CH(CH_3)_2)CO_2CH_2Ph$, $NHSO_2CH_2Ph(4\text{-}C(CH_3)_3)$,
$NHSO_2CH_2Ph$, $NHNHPh(2\text{-}F)$, $NHCH_2Ph(4\text{-}CF_3)$, $NHPh(4\text{-}OCH_2Ph)$,
$NHPh(4\text{-}SCH_3)$, $NHCH(CH_2Ph)CO_2CH_2CH_3$,
$NHCH(CH_2Ph)CO_2CH_3$, $NHCH_2Ph(4\text{-}OCH_3)$, $NHCH_2\text{-}1\text{-}naphthyl$,
$NHPh(4\text{-}F)$, $NHCH_2Ph(2\text{-}F)$, $NHCH_2CH(Ph)OH$, $NHCH_2CH_2Ph(4\text{-}F)$,
$NHC(CH_3)_2CH_2Ph(3\text{-}F)$, $NHPh(3,4\text{-}diF)$, $NHCH_2Ph(3\text{-}CH_3)$, $NHNH(3\text{-}CH_3)Ph$, $NHCH_2Ph(2\text{-}Cl)$, $NHCH_2Ph(2,4\text{-}diCl)$, $NHNHPh(4\text{-}CH_3)$,
$NHCH_2Ph(4\text{-}Cl)$, $NH(CH_2)_3Ph$, $NHCH_2CH_2Ph(4\text{-}Cl)$,
$NHCH_2CH_2N(CH_3)Ph$, $NHCH_2Ph(3\text{-}CF_3)$, $NHCH_2Ph(2\text{-}CF_3)$,
$NH(CH_2)_4Ph$, $N(CH_3)CH(CH_3)CH(CH_3)Ph$,
$N(CH_3)CH(CH_3)CH(CH_3)Ph$, $N(CH_2Ph)(CH_2)_3CH_3$, $NHOCH_2Ph$,
$NCH_2Ph(2,6\text{-}diF)$, $N(CH_3)CH(CH_3)Ph$, $NHCH(CH_3)Ph$,
$N(CH_3)CH_2Ph$, $NHCH_2Ph(3,4\text{-}diCl)$, $N(CH_3)CH(CH_3)Ph$,

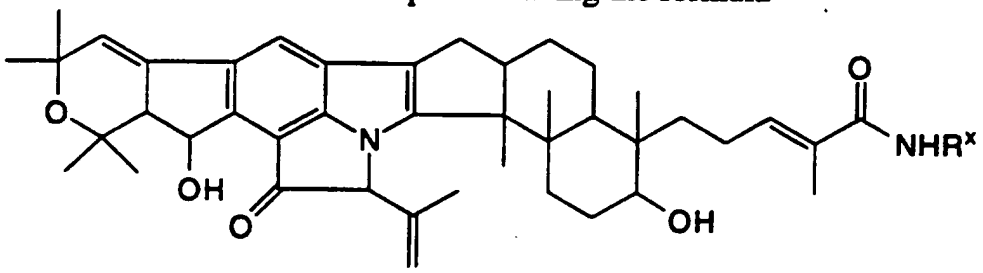


17. A compound having the formula



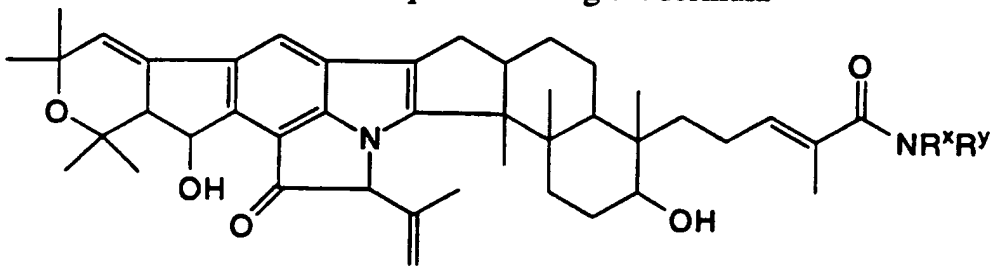
wherein R8 and R9 are hydrogen and separated by a double bond or R8 is hydroxy, R9 is hydrogen and separated by a single bond and NR^XR^Y is as defined in Claim 14.

18. A compound having the formula

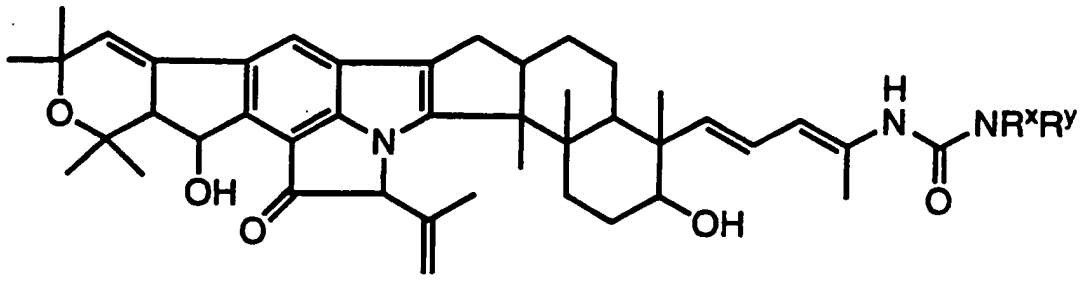


wherein R^X is as defined in Claim 13.

19. A compound having the formula

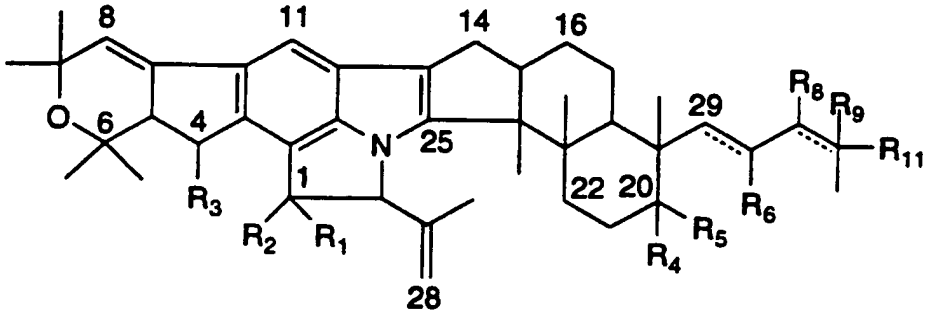


wherein NR^XR^Y is as defined in Claim 14.



wherein NR^xR^y is as defined in Claim 14.

24. A compound having the formula



where R_1 - R_6, R_8 and R_9 are as defined in Claim 1;

R_{11} is (1) COCl,

(2) CON_3, or

(3) NCO.

25. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

26. A composition of Claim 25 further comprising an anthelmintic agent.

27. A composition of Claim 26 wherein said anthelmintic agent is selected from ivermectin, avermectin, abamectin, emamectin, eprinamectin, doramectin,

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/US96/03611

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/40, 31/425, 31/445, 31/495; C07D 405/06, 487/16
US CL :514/233.2, 255, 322, 365, 397; 544/142, 310; 546/199; 548/417
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/233.2, 255, 322, 365, 397; 544/142, 310; 546/199; 548/417

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Structure

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,399,582 A (A. W. DOMBROWSKI ET AL.) 21 March 1995, columns 1-2, compounds 1-3.	1-3, 5-6, 11-12, 15, 25-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
10 MAY 1996	20 MAY 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Jacqueline Haley Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*